CFTRI-MYSORE
5143
Clinical pharmac..

F.C

CLINICAL PHARMACOLOGY

"Patients may recover in spite of drugs or because of them."

DR. J. H. GADDUM, 1959.

"The desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures. It is really one of the most serious difficulties with which we have to contend."

SIR WILLIAM OSLER, 1894.

"The ingenuity of man has ever been fond of exerting itself to varied forms and combinations of medicines."

DR. WILLIAM WITHERING, 1785.

CLINICAL PHARMACOLOGY

by

D. R. LAURENCE, M.D., M.R.C.P.,
Senior Lecturer in Applied Pharmacology, Department of Pharmacology, University College, and Medical Unit, University College Hospital Medical School, London,

and

R. MOULTON, M.B.,
Lately Research Assistant, Medical Unit, University College Hospital Medical School, London.

LITTLE, BROWN AND COMPANY - BOSTON
1960

5143

Lx3 N60

CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE * MYSORE *
LIBRARY
5/11/62

ALL RIGHTS RESERVED

This book may not be reproduced by any means, in whole or in part, without the permission of the Publishers.

First published 1960
© *J. & A. Churchill Ltd.*

CFTRI-MYSORE
5143
Clinical pharmac

Printed in Great Britain

PREFACE

THIS book is intended primarily for medical students in their clinical years and for those newly qualified, but it is hoped that this survey of the principal drugs, with details of their use and pharmacology, may be helpful to some postgraduate students and general practitioners.

Most books of moderate size confine themselves either to discussing the pharmacology of drugs without giving enough information for them to be selected and used effectively, or else they confine themselves to practical therapeutics and ignore the pharmacological background, without which efficient use of many drugs is difficult, or even impossible. It is nowadays too much to expect the heavily overburdened student to consult and integrate two works, one not always clearly related to clinical practice and the other often as arbitrary, and as apparently empirical, as a cookery book. This book is offered as a reasonably brief solution to the problem of combining practical clinical utility with some account of pharmacology.

It is not possible, of course, for two authors to cover the whole field of drug therapy from their own knowledge and experience, and in the subsequent section of acknowledgements we pay tribute to those who have generously helped us.

The decision to try to include sufficient practical details to enable drugs to be correctly used has inevitably made substantial parts of the book tedious. In addition, it has been thought necessary to mention many drugs of doubtful merit, and what have been aptly called "me-tooers", in order to enable a choice to be made from amongst the huge number of drugs or preparations of drugs thrust at the clinician by a vigorous pharmaceutical industry. The sensible student will readily see which sections of the book he can, and *should* neglect in his general reading, and use them solely for reference when the responsibility of choice and administration becomes his. He will realise too that he can ignore drug dosage and other such details until this time, for the only way to fix drug doses in the mind is by the actual prescribing of them.

No attempt has been made to supply a complete bibliography, but references are given at the end of each chapter. These have been largely selected for their interest, and the alert and intelligent medical student will appreciate that the contact with original minds which such reading affords is instructive, entertaining and sometimes even exciting. He will therefore choose an occasional paper on a topic that interests or amuses him and will read it as relaxation from the study of textbooks. The titles of the references, which are chiefly in the most accessible journals, are supplied to aid his choice. The doltish student does not read prefaces and so will not see these words, and in any case no amount of exhortation would make him appreciate what he is missing by never looking at original work and seeing how problems are tackled and knowledge obtained.

References to some reviews and source books are also included.

Direct quotation is used rather frequently in this book because, where a point has been well made by an original observer or thinker, there are excellent reasons for not interposing the mind of another.

Reasons for using non-proprietary drug names instead of the sometimes more familiar proprietary names, and for using the metric system for dosage throughout, are given in Appendix A. The index includes an inevitably incomplete range of proprietary names.

D. R. LAURENCE
R. MOULTON

ACKNOWLEDGEMENTS

THE authors are especially grateful to Professor M. L. Rosenheim, who has read the whole book and has given a lot of invaluable help. Great assistance with special sections has also been received from Drs. H. A. Burt and R. E. Bonham Carter, Professors C. E. Dent and A. C. Dornhorst, Mr. D. B. Griffiths, Drs. T. Honey, A. Jarrett, W. S. S. Ladell, J. D. Martin, H. Nicholson, D. A. Pond, T. A. J. Prankerd, E. A. Blake Pritchard, E. J. Ross, A. G. Spencer, Joan Stokes, G. I. M. Swyer, K. Sykes, E. Gwynne Thomas, W. R. Trotter, J. Walters, T. D. Whittet and O. Wrong.

Much of any merit that this book may be found to have is due to the generosity of those named above in putting their practical experience of the use of drugs at the authors' disposal. Responsibility for any errors rests with the authors, not with their advisers. In addition permission to quote directly from the writings of some authorities has been generously granted, and we thank them and their publishers for this. The names are acknowledged individually in the text.

CONTENTS

Chapter *Page*

1 Drug Therapy, Placebos and Tonics 1

2 Development of New Drugs, Therapeutic Trials . . 9

3 Chemotherapy and Chemotherapeutic Agents . . 18

4 Chemotherapy of Individual Diseases 54

5 Corticotrophin, Adrenocortical Hormones . . . 87

6 Hypnotics, Sedatives, Anticonvulsants 101

7 Anæsthetics, Neuromuscular Blocking Agents, Local Analgesics 121

8 Analgesics, Pain, Rheumatism 151

9 Drug Addiction, Tobacco, Alcohol 183

10 Drugs in Mental Disorder, Psychotomimetics . . 200

11 Antitussives, Expectorants, Anti-emetics . . . 214

12 Analeptics 222

13 Cholines and Anticholines 228

14 Sympathomimetics 249

15 Hypotensive and Vasodilator Drugs 262

16 Digitalis, Quinidine, Procainamide 284

17 Diuretics 304

18 Antacids, Purgatives, Constipation and Diarrhœa . . 315

19 Histamine and Antihistaminics 330

20 Vitamin K and Anticoagulants 337

21 Pituitary and Sex Hormones; Ergot 351

22 Thyroid Hormones and Antithyroid Drugs . . . 365

23 Insulin and Diabetes 375

24 Iron, Cyanocobalamin, Folic Acid 385

Chapter *Page*
25 Vitamins A, B, C, and D 398
26 Nucleotoxic Drugs 409
27 Drugs Acting on the Skin 416
28 Poisoning and Chelating Agents 429
29 General Pharmacology, Unwanted Effects of Drugs . 434
Appendix A Weights and Measures 450
Appendix B Dosage of Antimalarial Drugs . . . 457
Appendix C Surgery in Diabetic Patients 459
General References 461
Index 462

Chapter 1

DRUG THERAPY, PLACEBOS AND TONICS

DRUG THERAPY

Before treating any patient with drugs the doctor should have made up his mind on four points:—

1. Whether he should interfere with the patient at all and if so—
2. What alteration in the patient's condition he hopes to achieve.
3. That the drug he intends to use is capable of bringing this about.
4. What other effects the drug may have and whether these are likely to be harmful.

Mere accumulation of factual knowledge from books about drugs does not confer an ability to use drugs wisely, although wisdom cannot be attained without such knowledge.

Whenever a drug is given a risk is taken; it is often so small that second thoughts are hardly necessary, but sometimes it is substantial. The doctor must weigh up the likelihood of gain for the patient against the likelihood of loss. There are often insufficient data for an infallible decision to be reached, but a decision must be made none the less. The patient's protection lies in the doctor's knowledge of the drug, his knowledge of the disease, and his experience of both, together with his knowledge of the patient. For instance, in typhoid fever the risk of inducing aplastic anæmia with chloramphenicol is far less than the risk of dying from the untreated disease. In less dangerous infections the decision is less easy, and should chloramphenicol be used without mishap in, say, bronchitis, it may leave the patient so sensitised that a second or third course may prove fatal. It is impossible to be sure of the magnitude of such a risk.

In some diseases in which drugs will ultimately be needed they may not benefit the patient in the early stages. For example, a victim of early Parkinsonism may be but little inconvenienced by the disease, and the premature use of drugs, whilst perhaps reducing tremor or rigidity, can exact such a price in increased fatiguability, languor and constipation that the patient may prefer his untreated state. To attempt to antagonise the side-effects by other drugs is likely to be unsuccessful at worst, and unsatisfactory at best. Drugs very seldom cancel each other out exactly. It is worth remembering that a feeling of languor which may be merely a slight inconvenience to a manual worker, may totally disable a man who lives by his intellect. The most shameful act in therapeutics, apart from killing the patient, is to cause disease in a patient who is but little disabled or who is suffering from a self-limiting disorder. Such iatrogenic disease induced by misguided treatment, is far from rare.

If the doctor is temperamentally an extremist, he will do less harm by adopting therapeutic nihilism than by optimistically overwhelming his patients with well-intentioned polypharmacy. The latter course is the easier to follow because it gives more immediate satisfaction to the patient, his family and indeed to the doctor himself. All are able to feel cosily that it is clear that the doctor is doing all he can, which usually means a great deal more than is wise. Habitual polypharmacy is sure to blur the outline of rational thought which should precede the use of any drug, and both doctor and patient will be the worse for this.

If in doubt whether or no to give a drug, don't.

In 1917, Sollmann felt able to write "Pharmacology comprises some broad conceptions and generalisations, and some detailed conclusions, of such great and practical importance that every student and practitioner should be absolutely familiar with them. It comprises also a large mass of minute details, which would constitute too great a tax on human memory, but which cannot safely be neglected."*

If the last sentence was true when it was written, it is many times more true now. The selection of useful drugs from the multitude, not only offered to, but actually pressed upon the doctor by skilful advertising, is a matter of very great importance. The doctor's aim must be not merely to give the patient what will do him good, but to give him *only* what will do him good, or at least more good than harm.

It has been recorded from a large hospital in the U.S.A. that of 1,000 patients admitted to the wards, 50 suffered *major* toxic reactions consequent to diagnostic or therapeutic measures before or after admission.†

In England and Wales in two years, there were 302 "*fatal* therapeutic misadventures due to adverse reaction to drug or therapy", excluding those due to anæsthesia.‡

They included:—

phenylbutazone	9	chiefly blood dyscrasias
chloramphenicol	13	chiefly blood dyscrasias
sulphonamides	17	chiefly blood dyscrasias
insulin	36	18 due to hypoglycæmia, with coma or shock
chlorpromazine	4	two due to hepatic toxicity
penicillin	13	mostly hypersensitivity reactions
anticoagulants	9	all hæmorrhages

---

* Sollmann, T. A. (1917). Manual of Pharmacology. Philadelphia: Saunders.
† Barr, D. P. (1955). *J. Amer. med. Ass.*, **159**, 1452.
‡ Registrar General's Statistical Review of England and Wales, 1956, Part 3. Commentary. London: H.M.S.O.

In addition deaths were registered as due to: chloral (purpura), benzhexol (aplastic anæmia), phenytoin (2, aplastic anæmias), gold (11, mainly blood dyscrasias), hydrocortisone (2, septicæmias following injection).

These figures are almost certainly underestimates for there is a very natural reluctance amongst doctors to attribute a patient's death to "therapy" and death is attributed to disease if it is at all reasonable to do so.

In addition to the fatalities there is the undoubtedly huge body of patients merely made ill by drugs. The medical profession is contributing significantly to disease, although it can justly be contended that the disease caused by doctors is far outweighed by the benefits that they purvey. There is still, however, the obligation to strive to obtain the maximum good with the minimum harm.

It is not suggested that all the accidents reported were avoidable; but it is difficult to resist the conclusion that an unnecessarily large number of people suffer nowadays from iatrogenic disease and that a part of it could be avoided by the more thoughtful use of drugs.

New drugs especially should be treated with suspicion. They should not be used widely until properly designed clinical trials have been carried out, especially not in patients with relatively non-serious disease. Patients with recurrent boils have died from chloramphenicol; some with hypertension have committed suicide as a result of rauwolfia-induced depression; others with rheumatoid arthritis have died from agranulocytosis due to phenylbutazone.

Sir Anthony Carlisle, in the first half of the 19th century, said that [illegible] "an art founded on conjecture and improved by murder". [illegible] medicine has advanced so rapidly, there is still a ring of truth in that statement to anyone who follows the introduction of new drugs and observes how, after the early enthusiasm, the reports of serious toxic effects inevitably appear.

Another cryptic remark of this therapeutic nihilist was "Calomel is poison and digitalis kills people." This pejorative remark is of interest because the latter is one of the few essential drugs in modern therapy. It is essential because it is potent, and since it is potent it can kill when used ignorantly or carelessly. William Withering in 1785 laid down rules for the use of digitalis which would serve today. Neglect of these rules resulted in needless suffering for patients with heart failure for more than a century until the therapeutic criteria were rediscovered. Any drug that is really worth using can do harm, and it is an absolute obligation on the doctor to use only drugs about which he has troubled to inform himself. The following report of a coroner's inquest shows the reality of this:

" . . . an inquest has been held on a woman who died from internal hæmorrhage due to dicoumarol which had been given for thrombosis in the leg veins. The doctor is reported to have said that he gave the dose recommended in the manufacturer's literature; he confessed his ignorance of the dangerous properties of dicoumarol and complained that these were not mentioned in the instructions for use."*

Irresponsibility does not always flaunt itself as in this case, but it contributes greatly to the misuse of drugs, not only by overdose, but by inadequate dosage when the doctor is uninformed and does not have clear aims. In addition there is the small but constant death rate from all-too-human carelessness of the kinds shown in the table.

Fatal Therapeutic Misadventures due to Mistakes in Drug Administration in England and Wales, 1954-6†

Drug	*Nature of Misadventure*
	Medically administered
barbitone	given in mistake for sulphasomidine
mersalyl	injected instead of combined diphtheria, pertussis, tetanus antigen
potassium chlorate	given in mistake for sodium chloride
sodium carbonate	given by enema instead of barium salt (two cases)
syrup of chloral	nurse mistook the bottle
	Self-administered
adrenaline & atropine	used as nasal-drops instead of spray as prescribed
oxalate	taken in belief of medicinal property
Sulfex (a mixture of a sulphonamide and amphetamine as nasal-drops or spray)	did not know effects of drug
	Administration not stated
amethocaine	in error for procaine
camphor & turpentine	in mistake for "medicine"
mercury	instead of a radio-opaque contrast medium recommended for use in the subarachnoid space
turpentine	in error

Effective therapy depends not only on the correct choice of drugs but also on their correct use. This latter is sometimes forgotten and a drug is condemned as useless when it has been used in a way which absolutely precluded a successful result.

---

* Editorial (1949). *Lancet*, (*i*), 698.

† Based on a table in Registrar-General's Statistical Review of England and Wales 1956, Part 3. Commentary. London: H.M.S.O.

PLACEBOS AND TONICS

A placebo* is a medicine which is given to benefit or please a patient, not by any pharmacological actions which it might have, but by psychological means. It is a vehicle for cure by suggestion, and often an unsatisfactory one. The use of drugs for this purpose is a confession of failure by the doctor. Failures however are sometimes inevitable and an absolute condemnation of the use of placebos on all occasions would be unrealistic for, "to decline to humour an elderly 'chronic' brought up on the bottle is hardly within the bounds of possibility" (*1*).

Placebos are usually given to patients with mild psychological disorders who attribute their symptoms to physical disease. There is no doubt that alleviation can sometimes be achieved but it is often only temporary, and may make any subsequent attempt to face reality more difficult. The patient, not unreasonably, interprets the advice to take medicine as meaning that the doctor admits a physical basis for the symptoms; so that when, later on, an attempt is made to attribute a psychological cause this will not be accepted. They may also be used in patients with chronic incurable diseases when they need a prop to sustain their courage. Drugs used against specific symptoms, such as pain or diarrhœa, are not, of course, placebos, although they may have additional psychological effects unrelated to their pharmacological action, according to the amount of suggestion provided by the prescriber, consciously or unconsciously.

Placebos should only be prescribed after a serious attempt to avoid using them has failed and then only for a brief time; the placebo should consist of a substance both innocuous and cheap. Having admitted the legitimacy of their use, however rarely, it is necessary to advise a choice of substances.

"Those who have qualms of conscience about prescribing pharmacologically useless medicines tend to use semi-placebos, such as vitamins, in the vague hope that these may do some good. This is wrong, for thereby the prescriber deceives himself as well as the patient. If deception there must be, says Leslie (*3*), let it be wholehearted, unflinching, and efficient. A placebo medicine should be red, yellow or brown; for blue and green are colours popularly associated with poisons or with external applications. The taste should be bitter but not unpleasant. Capsules should be coloured, and tablets either very small (on the *multum in parvo* principle) or impressively large; they should not look like everyday tablets such as aspirin"(*1*).

---

* The term is also used to mean a dummy tablet when this is used as a control in the scientific evaluation of drugs.

Potent drugs should never be used as placebos, nor should expensive ones whether it is the patient or the State who pays.

The following two mixtures are readily available and will serve the purpose:—

Compound Tincture of Cardamom, B.P., this also contains cochineal, cinnamon, caraway and glycerin. It has a taste and colour well adapted to deceit and the dose is 1 to 2 ml. in 15 ml. (tablespoonful) of water.

Gentian and Acid Mixture, B.P.C., the dose is 15 to 30 ml.

Wolf has made a study of the "pharmacology of placebos"(*2*, *2a*). He points out that the effects of a drug on an intact organism may bear no relation to the pharmacological actions found on isolated-organ preparations. The effects of a drug depend on:—

1. The physiological state of the organ on which the drug is to act, whether, for instance, it is over- or under-active.

2. The setting in which the agent is administered, including the route of administration, the presence of the experimenter and the effects of suggestion implied or expressed.

3. Conditioning circumstances and previously established habits of reaction.

The following quotation illustrates some of these points:—

". . . a 28-year-old female had had recurrent nausea for several months. . . . A kymographic recording from her stomach revealed the characteristic absence of contractile activity during nausea. After a suitable control period she was given 10 cc. syrup of ipecacuanha directly into the stomach through a Levine tube. Repeatedly on previous occasions this amount of ipecacuanha when swallowed had induced nausea and vomiting. On this occasion, however, not tasting and not knowing what she had been given, she was told that the agent would abolish her nausea; within 30 minutes nausea was gone and small waves of contraction were recorded from the stomach. Sixty minutes later when nausea had recurred with associated gastric hypomotility a second dose of ipecacuanha was introduced into the Levine tube, this time with the reassurance that the nausea would be effectively abolished. Nausea disappeared again in 15 minutes and gastric contractions were resumed. No further nausea was experienced that day" (*2*).

This dramatic demonstration shows that psychological effects may actually reverse pharmacological effects. "It is likely that this mechanism is operative in part in any enthusiastically pursued therapeutic regime. . . . It has even been shown experimentally that the threshold for pain perception may be greatly raised by suggestion" (*2*).

It is of great importance that everyone who administers drugs should be aware that his attitude to the treatment may greatly influence the result. Undue scepticism may prevent a drug from achieving its effect and enthusiasm or confidence may potentiate the pharmacological actions of drugs.

There is every reason for the doctor to cultivate techniques for the psychological potentiation of drugs, for his aim is to help the patient, but it is essential that he should be aware of what he is doing and not deceive himself about the power of his remedies.

Tonics are substances with which it is hoped to strengthen those so weakened by disease, misery, over-indulgence in play or work, or by physical or mental inadequacy, that they cannot face the stresses of life. The essential feature of this weakness is the absence of any definite recognisable defect for which there is a known remedy. There can be very few doctors who believe that there is any pharmacological basis for a tonic effect. Benefits are attributable to placebo-effects and it is to be hoped that explanation and reassurance will eventually take the place of "bottles of medicine". Many people expect a tonic from their doctor following any illness and they would be, indeed they are, sceptical and shocked when told that the benefits that they feel are not the result of pharmacological action.

If either the doctor or the patient believes in tonics to such a degree that one has to be prescribed, it may be chosen from those in the B.N.F. which include Strychnine Mixture, B.P.C., and Strychnine and Iron Mixture, B.N.F. Strychnine is a traditional tonic and long usage has shown it to be innocuous when used in this small dose, but the dangers of incompatibility make its use in extempore prescriptions inadvisable. There are innumerable proprietary tonics, some of which contain highly active drugs; these should be avoided. The indiscriminate use of vitamins as tonics is widely advocated by pharmaceutical firms. The use of ascorbic acid and the B group of vitamins for this purpose is harmless, though sometimes expensive, but vitamin D should never be prescribed as a tonic as it can cause serious toxic effects. There is no scientific evidence that phosphates added to wine or offered as a concentrated solution of "neurophosphates" have any therapeutic effects other than by a placebo action.

Guide to Further Reading on Placebos

(*1*) Editorial (1954). The humble humbug. *Lancet*, (*ii*), 321.

(*2*) Wolf, S. (1950). Effects of suggestion and conditioning on the action of chemical agents in human subjects—the pharmacology of placebos. *J. clin. Invest.*, **29**, 100.

(*2a*) Wolf, S. (1959). The pharmacology of placebos. *Pharmacol. Rev.*, **11**, 689.

(3) Leslie, A. (1954). Ethics and practice of placebo therapy. *Amer J. Med.*, **16**, 854.

(4) Ayman, D. (1930). An evaluation of therapeutic results in essential hypertension. *J. Amer. med. Ass.*, **95**, 246.

(5) Beecher, H. K. (1955). The powerful placebo. *J. Amer. med. Ass.*, **159**, 1602.

(6) Joyce, C. R. B. (1959). Consistent differences in individual reactions to drugs and dummies. *Brit. J. Pharmacol.*, **14**, 512.

(7) Knowles, J. B., and Lucas, C. J. (1960). Experimental studies of the placebo response. *J. Ment. Sci.*, **106**, 231.

Chapter 2

DEVELOPMENT OF NEW DRUGS, THERAPEUTIC TRIALS

THE DEVELOPMENT OF NEW DRUGS

Doctors should have some idea of how the new drugs they are offered are devised or discovered.

More new drugs are developed in commercial pharmaceutical laboratories than in academic institutions. This is because academic research workers are principally interested in fundamental problems and are not willing to devote long, tedious months to applying or supervising routine screening tests to series of chemical compounds made in profusion by organic chemists. They do however supply much of the basic knowledge which is applied to practical purpose by the drug firms. The result is a symbiosis between the two organisations and a steadily growing stream of new drugs offered for clinical trial following examination of their actions on animals. It is not meant to imply that no fundamental research is done in commercial organisations.

Chance still plays a large part in the discovery of new drugs, but with the present rapid advances in knowledge of the relationship between chemical structure and pharmacological action, drugs are now developed more rationally.

Vane (*1*) has described how the pharmacologist tests new chemical compounds to discover whether they may have any future as drugs. Technicians, each trained to perform a single test, run the screening laboratory under his direction.

Each chemical compound is put through a series of tests designed to cover a wide range of pharmacological actions as economically as possible, and so expose any effects which might be of use in medicine.

Such routine tests include those to elucidate:—

Possible Useful Actions. The effect of the substance on:—

1. The blood pressure and respiration of an anæsthetised cat or dog. To reveal any effect on medullary centres or cardiovascular or respiratory systems.

2. An isolated piece of intestine of guinea-pig or rabbit. To reveal actions on smooth muscle.

3. An isolated nerve-muscle preparation. To reveal effects on peripheral nerve, voluntary muscle or neuromuscular junction.

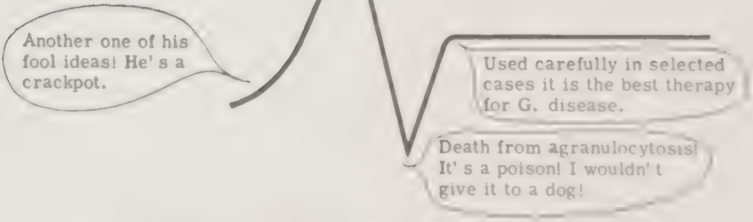
4. Rats or mice subjected to mild experimental pain, *e.g.* heat, electric shock. To reveal analgesic properties.

Toxic Effects. The substance is also given to groups of mice, to determine the lethal dose in acute and chronic experiments and to reveal the extreme of activity of the compound. The symptoms, such as convulsions or paralysis, may give further information.

When a notion of the properties of a compound has thus been obtained, it is either discarded or more detailed experiments are designed to elucidate its actions. If it seems that the substance may have clinical utility long-term toxicity tests are begun to reveal effects that may have delayed onset, *e.g.* liver damage, carcinogenesis.

This empirical approach is essential if important drug actions are not to be missed. For example, the neuromuscular-blocking action of suxamethonium chloride was missed 50 years ago because it was tested on curarised animals. This should not happen now since pharmacologists are aware both of their own ignorance and of the possibilities of pharmacological action, and take the steps described above to avoid such occurrences.

To combine empiricism with scientific planning is necessary at present, but as time passes the amount of the former will decrease until the day comes when drugs will be made to order.


Another one of his fool ideas! He's a crackpot.
Gee it's wonderful! It's simple, cheap and cures magically.
Death from agranulocytosis! It's a poison! I wouldn't give it to a dog!
Used carefully in selected cases it is the best therapy for G. disease.

Oscillations in the development of a drug.
(By courtesy of Dr. Robert H. Williams and the Editor of *J.A.M.A.*)

When an interesting compound has been found, the detailed pharmacology is worked out in specially designed experiments, which will also reveal the duration of action, the fate in the body, the routes by which it may be administered and what are effective antagonists to its effects. If the toxicity tests are satisfactory the drug may then be offered to the clinician, who may cautiously administer it to man for the first time. Unfortunately it does not follow that effects in man will be identical with those in animals, and very great care and a sense of responsibility are needed.

It is fruitless to deplore animal experiments (*2*); new drugs stem from them and will continue to do so, and man is indebted to animals for much help. One of the greatest difficulties of the laboratory pharmacologist is to design his animal experiments to yield the maximum information and yet still be relevant to human physiology and disease. It is, for example, particularly difficult to design animal experiments to test drugs for their possible efficacy in human psychological disorders but relatively easy to test them for anticoagulant effects.

THERAPEUTIC TRIALS

> "In your ideas of the powers of remedies do not be too sanguine for you are liable to continued disappointment."
> (Sir Anthony Carlisle, 1824.*)

When preliminary clinical experiments have been done with a new drug in a responsible and ethical fashion, and if some evidence suggestive of clinical importance has been obtained, whether the drug opens up a completely new attack on a disease or whether it excels in effect or safety those drugs already in use, it is time to consider a larger scale trial to determine whether it has a place in therapeutics.

Pickering has written, ". . . therapeutics is the branch of medicine that, by its very nature, should be experimental. For if we take a patient afflicted with a malady and we alter his conditions of life . . . we are performing an experiment. And if we are scientifically minded we should record the results. Before concluding that the change for better or for worse in the patient is due to the specific treatment employed, we must ascertain . . . whether the result was merely due to the natural history of the disease . . . or whether it was due to some other factor which was necessarily associated with the therapeutic measure in question. And if, as a result of these procedures, we learn that the therapeutic measure employed produces a significant, though not very pronounced improvement, we would experiment with the method, altering dosage or other detail to see if it can be improved. This would seem the procedure to be expected of men with six years of scientific training behind them.

"But it has not been followed. Had it been done we should have gained a fairly precise knowledge of the place of individual methods of therapy in disease, and our efficiency as doctors would have been enormously enhanced" (*1*).

---

* DAVIES, J. L. (1952). Westminster Hospital. London: Murray.

In order to decide whether patients treated in one way are benefited more than those treated in another, there is no possibility of avoiding the use of numbers. The mere statement by a clinician that patients do better with this or that treatment is due to his having formed an opinion that more patients are helped by the treatment he advocates than by other treatments. The opinion is based on numbers, but having omitted to record exactly how many patients have been treated by different methods and having omitted to ensure that the only variable factor affecting the patient was the treatment in question only a "clinical impression", instead of a scientific fact, can be stated. This is a pity, for progress is delayed when convinced opinions are offered in place of convincing facts. The former, though not necessarily wrong, are unreliable, despite the great assurance with which they are often advanced. It has been pointed out that when the worth of a treatment, new or old, is in doubt there may be a greater moral obligation to test it critically than to go on prescribing it supported only by habit or wishful thinking (2).

Nearly 100 years ago Francis Galton saw this clearly. "In our general impressions far too great weight is attached to what is marvellous. . . . Experience warns us against it, and the scientific man takes care to base his conclusions upon actual numbers. The human mind is . . . a most imperfect apparatus for the elaboration of general ideas. . . . General impressions are never to be trusted. Unfortunately when they are of long standing they become fixed rules of life, and assume a prescriptive right not to be questioned. Consequently, those who are not accustomed to original enquiry entertain a hatred and a horror of statistics. They cannot endure the idea of submitting their sacred impressions to cold-blooded verification. But it is the triumph of scientific men to rise superior to such superstitions, to devise tests by which the value of beliefs may be ascertained, and to feel sufficiently masters of themselves to discard contemptuously whatever may be found untrue . . . the frequent incorrectness of notions derived from general impressions may be assumed. . . ."*

In order to test a treatment a well-designed therapeutic trial (a form of biological assay) is essential because, by giving a definite answer, it may save lives, time and money. This is true even if at first sight the requirements that will satisfy a statistician seem unduly complex, for the result will convince everyone instead of solely the author. It is essential to consult a statistician before starting a trial if disappointment and wasted effort are to be avoided. The requirements to obtain a clear answer vary enormously. In rheumatoid arthritis or in pain they are very stringent. However, in leukæmia a single recovery would be, and in tuberculous meningitis a single recovery was, rightly, considered to be highly significant. Advice from a statistician is not therefore invariably needed, but should be obtained if there is the slightest doubt on the matter, for the function of a statistician is to help the clinician to obtain a reliable result.

---

* Galton, F. (1879). Generic images. *Proc. Roy. Inst.*

In addition, the double-blind technique (defined below) should be used where possible whenever evaluation depends on other than strictly objective measurements. There are occasions when it might at first sight seem that criteria of clinical improvement are objective when in fact that is not so, for example the range of voluntary joint movement in rheumatoid arthritis has been shown to be greatly influenced by psychological factors, and a moment's thought shows why, for the amount of pain a patient will put up with is greatly influenced by his mental state. Assessment of progress of chest radiographs in pulmonary tuberculosis is also not free from bias, due to enthusiasm or lack of it, and in the classic Medical Research Council chemotherapy trials it was arranged that the radiologist commenting on the serial films should do so in ignorance of what treatment the patient was having.

The double-blind technique is "a control device to prevent bias from influencing results. On the one hand it rules out the effects of hopes and anxieties of the patient by giving both the drug under investigation and a placebo (dummy) of identical appearance in such a way that the subject (the first 'blind' man) does not know which he is receiving. On the other hand, it also rules out the influence of preconceived hopes of, and unconscious communication by, the investigator or observer by keeping him (the second 'blind' man) ignorant of whether he is prescribing a placebo or an active drug. At the same time, the technique provides another control, a means of comparison with the magnitude of placebo effects.

"The device is both philosophically and practically sound. In addition, perhaps because of the widespread attention it has attracted, or the magic quality it appears to have, the double-blind technique has been assumed to be a complete method of drug evaluation in itself. Indeed, it is often called the double-blind test. Many seem to believe that all that is necessary for a good clinical study is to use it, and, since it is relatively easy to apply, many are exploiting it in just this way. A number of papers emphasise in the very title that this type of control was used, not only as if the use of a control were worthy of special mention, but also as if to warn the reader in advance that a special type of insurance had been taken out to guarantee that the results about to be recounted were beyond reproach" (9).

Sometimes the double-blind technique is not possible because, for example, side-effects of an active drug reveal which patients are taking it, but it never carries a disadvantage, "only protection against spurious data".

The foregoing quotation refers to occasions when a dummy or placebo treatment would be used, but this is not invariably necessary or indeed ethical.

One important use of dummy treatment is in the avoidance of false negative conclusions in a trial where the negative result might be due to the fact that the method used is unsuitable and *incapable* of showing a positive effect. For example, a therapeutic trial of a new analgesic should consist of a comparison of the new drug with a known active analgesic as well as with a dummy. If all three treatments give the same result, a likely explanation is that the method used is incapable of distinguishing between an active and an inactive drug and so should be modified; whereas if only the new drug and the dummy are used and give identical results, there are two possible explanations, first that the method used is insensitive and second that the new drug has only placebo-effect, *i.e.* is pharmacologically inactive at the dose used.

It was found, for instance, in one trial in which angina pectoris was being treated and the progress of the disease determined by recording the frequently of attacks of pain, that 60% of patients improved over, on average, the first eleven weeks, regardless of whether they were receiving an active drug, a dummy (using double-blind technique) or no treatment at all. This meant that the method was less sensitive over this period and improvement genuinely due to a drug was masked, at least partially, until after the eleventh week. This general improvement regardless of drug therapy could partly be attributed to the establishment of a good psychological relationship between patient and physician (*14*). The double-blind technique is not, of course, used with drugs fresh from the laboratory whose dose, effects and human toxicity are uncertain.

Sometimes in chronic disease it is possible to give a number of drugs to one patient thus conveniently using him as his own control, for example in Parkinsonism, hypertension, anxiety states. When this is done it is important to ensure that in a series of administrations each drug both precedes and follows each other drug the same number of times, to avoid the risk of systematic bias as a result of "carry-over" after a drug has ceased to be given. If in an analgesic trial a weak drug always follows a potent drug the weak drug may be dismissed as ineffective because the patient's standard has become influenced by the high degree of relief provided by the potent drug. The weak drug must precede as well as follow both the potent drug and the dummy if error is to be avoided. In acute diseases it is impossible to give more than one treatment to one patient and the controls must be other patients.

Bradford Hill defines the clinical trial as "a carefully, and ethically, designed experiment with the aim of answering some precisely framed question. In its most rigorous form it demands equivalent groups of patients concurrently treated in different ways. These groups are constructed by the random allocation of patients to one or other treatment. . . . In principle the method is applicable with any disease and any treatment. It may also be applied on any scale; it does not necessarily demand large numbers of patients" (*3*).

Three important points in the above definition may be stressed: "*Equivalent groups of patients.*" If the treatment groups differ significantly in age, sex, race, duration of disease, severity of disease or in any other possibly relevant factor, it will not be possible to attribute differences in outcome to the treatment under investigation, unless there is some way of eliminating the bias that has entered. The best way of getting equivalent groups is by allotting patients to them by "*random allocation*". To allot patients alternately is not satisfactory as the physician almost inevitably knows into what treatment group a patient will go whilst engaged in deciding whether the patient should enter the trial, and he may be unconsciously influenced by this if he has strong feelings about either the patient or the value of the respective treatments. With random allocation the treatment group into which the patient goes is only discovered after it has been decided to enter him in the trial. Sometimes "it may be considered embarrassing to have recourse to opening a sealed envelope—and still more to tossing a coin" if a decision has to be made in front of the patient, and randomisation can equally easily be achieved by a very simple mental trick (*8*).

Treatments must be carried out "*concurrently*", partly because of the desirability of randomisation and partly because diseases may vary in severity with time, virulence of an organism may change, especially in epidemics, the weather may influence respiratory and cardiac diseases or a hospital may even get a reputation, for good or ill, so that more or less severe cases may be sent to it.

Before commencing any therapeutic trial it is essential to formulate exactly the question that is to be answered. For example: "Is drug X capable of relieving the pain of osteoarthritis more or less completely, with greater or less side-effects and for a shorter or longer time than Codeine Compound Tablets, B.P.?" The question should be as simple as possible, for to try to discover too much can be a cause of failure, and it should be kept in mind throughout the whole process of designing the trial. Failure to set down at the start exactly what it is hoped to discover leads to muddle.

The aims of a clinical trial, not all of which can be attempted on any one occasion, are to decide:—

1. whether a treatment is of value,
2. how great its value is (compared with other remedies, if such exist),
3. in what types of patients it is of value,

4. what is the best method of applying the treatment, how often, and in what dosage if it is a drug,

5. what are the disadvantages and dangers of the treatment.

Ross, impressed by the number of articles which extolled some form of therapy but which did not give any acceptable evidence that it was effective, analysed a representative group of 100 medical papers according to one criterion, the use of adequate controls. He concluded that only 27% of published trials showed a definite result. "Other therapies *may* be effective, *but the papers do not show it or the reverse*" (*4*). It has also been significantly remarked that authors claim success in psychiatric treatment more often in uncontrolled studies (85%) than they do in studies in which controls have been used (19%) (*17*). Such wasted effort is appalling.

It is not always easy to decide when a true result has been obtained, even in an apparently well-designed trial (*9*). "Periodically it is observed that the introduction of a new drug is followed by a cluster of favourable reports of its therapeutic value. Later it is often discovered (but not always published) that the agent has no appreciable scientific therapeutic action. Then, as the agent has fallen into disuse, many have assumed that the authors of the favourable reports were either deluded or at least not sufficiently critical of their results. Actually, the favourable reports may have contained strong statistical evidence that the desired physiological change had been achieved. There is little reason to doubt that the results were real enough. The neglected possibility that may explain the later failure of the agent is that the good results were attributable, not to the pharmacological properties of the agent, but to very real and often powerful placebo-effects. In a recent study of inhibition of the cough reflex Hillis obtained an effect with placebos as great as that observed with 30 mg. of codeine" (*5*).

This brief account of some aspects of therapeutic trials may be sufficient to show with what care they must be designed. The possibilities of error are legion. Throughout this book there are references to examples of well-designed trials which show how the same principles are adapted to suit widely different circumstances. The reader is recommended to consult them both for instruction and entertainment and to pursue the subject further in the list of references on the next page.

Guide to Further Reading

On the Development of New Drugs

(*1*) **Vane, J. R.** (1956). The experimental approach to pharmacology. *Med. Press*, 235, 218.

(*2*) **Dale, Sir Henry** (1955). On humanity's rising debt to medical research. Stephen Paget Memorial Lecture. *Brit. med. J.*, 1, 1266.

On Therapeutic Trials

(*1*) Pickering, G. W. (1949). The place of the experimental method in medicine. *Proc. roy. Soc. Med.*, **42**, 229.

(*2*) Green, F. H. K. (1954). The clinical evaluation of remedies. *Lancet*, (*ii*), 1085.

(*3*) Hill, B. (1955). Principles of Medical Statistics. London: The Lancet. Everyone thinking of doing a therapeutic trial should read the relevant chapters of this book. They are brief. There is an appendix of random sampling numbers.

(*4*) Ross, O. B. (1951). Use of controls in medical research. *J. Amer. med. Ass.*, **145**, 72.

(*5*) Wolf, S., and Pinsky, R. H. (1954). Effects of placebo administration and occurrence of toxic reactions. *J. Amer. med. Ass.*, **155**, 339.

(*6*) Beecher, H. K. (1953). Analgesic power and the question of "acute tolerance" to narcotics in man. *J. Pharmacol. exp. Therap.*, **108**, 158.

(*7*) Gaddum, J. H. (1954). Clinical pharmacology. *Proc. roy. Soc. Med.*, **47**, 195.

(*8*) Doll, R. S. (1959). Practical problems of drug trials in clinical practice. *In* Quantitative Methods in Human Pharmacology and Therapeutics. Ed. D. R. Laurence. London: Pergamon Press.

(*9*) Modell, W., and Houde, R. W. (1958). Factors influencing clinical evaluation of drugs with special reference to the double-blind technique. *J. Amer. med. Ass.*, **167**, 2190.

(*10*) Beecher, H. K. (1958). Experimentation in Man. Springfield: Thomas.

(*11*) Medical Surveys and Clinical Trials (1959). Ed. L. J. Witts. London: Oxford University Press.

(*12*) Herdan, G. (1955). Statistics of Therapeutic Trials. Amsterdam: Elsevier.

(*13*) Kennedy, A. (1959). The psychology of clinical trials. *Pharm. J.*, **128**, 5 and 23.

(*14*) Cole, S. L., and Griffith, G. C. (1958). Assay of antianginal agents —the rapport method. *J. Amer. med. Ass.*, **168**, 275.

(*15*) Gold, H. (1959). Experiences in human pharmacology. *In* Quantitative Methods in Human Pharmacology and Therapeutics. Ed. D. R. Laurence. London: Pergamon Press.

(*16*) Fox, T. F. (1959). The ethics of clinical trials. *In* Quantitative Methods in Human Pharmacology and Therapeutics. Ed. D. R. Laurence. London: Pergamon Press.

(*17*) Foulds, G. A. (1958). Clinical research in psychiatry. *J. Ment. Sci.*, **104**, 259.

(*18*) Clinical Evaluation of New Drugs (1959). Ed. S. O. Waife and A. P. Shapiro. New York: Hoeber-Harper.

Chapter 3

CHEMOTHERAPY AND CHEMOTHERAPEUTIC AGENTS

THE term chemotherapy is used for the drug treatment of parasitic infections by destroying or removing the parasites (bacteria, viruses, protozoa, worms) without injuring the host. The use of the term to cover all drug, or synthetic drug, therapy removes a distinction which is convenient to the clinician.

Chemotherapy has been practised empirically since ancient times. The neolithic Danes cultivated chenopodium, although what they did with it is unknown. The Ancient Greeks used male fern, and the Aztecs chenopodium, as intestinal anthelminthics. The Ancient Hindus treated leprosy with chaulmoogra; there are numerous other examples. For hundreds of years moulds have been applied to wounds, but, despite the introduction of mercury as a treatment for syphilis (16th century), and the use of cinchona bark against malaria (17th century), the real history of modern chemotherapy does not begin until the late 19th century. With the knowledge of bacterial and protozoal causation of diseases and the development of techniques for infecting laboratory animals, scientific therapeutic experiments could be performed. These animal experiments were not subject to the restrictions of clinical therapeutics so that toxicity could be risked and large numbers of infections treated under controlled conditions. In addition, acceptance of archaic authority and belief in magic were on the wane and a scientific approach to medical problems was becoming less rare.

It is not surprising that the differential staining of tissues and bacteria should have been the basis of early chemotherapeutic research for it was an obvious instance of chemicals affecting parasite and host differently. Aniline dyes were used for staining and, when it was shown that these dyes could also kill bacteria, Ehrlich, already interested in the differential staining of leucocytes, tried the effect of dyes on infected experimental animals. In 1891 he cured experimental malaria in guinea-pigs with methylene blue, but it was less effective than quinine. In 1904 he controlled trypanosome infections in mice with another dye, trypan red, but it was ineffective in other species.

Ehrlich thus developed the idea of chemotherapy and he also gave it its name. In 1906 he wrote: "In order to use chemotherapy successfully we must search for substances which have an affinity for the cells of the parasites and a power of killing them greater than the damage such substances cause to the organism itself, so that the destruction of the parasite will be possible without seriously hurting the organism. This means we must strike the parasites and the parasites only, if possible, and to do this we must learn to aim, learn to aim with chemical substances!" (5).

Knowledge of the relationship between chemical structure and pharmacological action (*i.e.* learning to aim with chemicals) has steadily increased until at last it is being effectively applied to the development of new drugs.

By 1906 it was clear that chemotherapy was a practical proposition and not the fantasy that some eminent contemporaries declared it. Inorganic arsenic had been shown to clear trypanosomes from the blood of infected horses and this probably inspired Ehrlich to examine organic arsenicals. This study resulted in the introduction of arsphenamine (Salvarsan) for the treatment of syphilis. This was soon followed by neoarsphenamine (Neosalvarsan) which was widely used until after the introduction of penicillin in 1941.

Ehrlich also introduced the concept of a "chemotherapeutic index" which was the "maximum tolerated dose" divided by the "minimum curative dose" of a drug. For clinical purposes this index is not calculated since the exact values of the doses are never known, but clearly penicillin has a high index and is, therefore, a relatively safe drug while arsenic has a low index and so is dangerous. This concept of Ehrlich's is valuable and now plays a part in everyday thought about drugs. After neoarsphenamine there was a lull. Then the antimalarials pamaquine and mepacrine were developed from dyes and in 1935 the first sulphonamide, linked with a dye, was introduced as a result of empirical experiments by Domagk.

The results obtained with sulphonamides in puerperal sepsis, pneumonia and meningitis were dramatic and caused a violent reorientation of medical thought. Up to that time chemotherapy had been virtually confined to protozoa and metazoa, spirochætes being considered a special case. The prospect of killing pyogenic bacteria in the body had seemed to be unattainable.

In 1929, six years before the discovery of the sulphonamides, Fleming, whilst studying staphylococcal variants, found one of his culture plates contaminated with a fungus which destroyed surrounding bacterial colonies. This accidental rediscovery of the long-known ability of penicillium fungi to suppress the growth of bacterial cultures was now followed up. Fleming investigated the properties of "mould broth filtrates" which he named "penicillin" for brevity. He described penicillin as an antiseptic more powerful than phenol which yet could safely be applied to the tissues. The name "penicillin" has since been applied to the pure antibiotic substances obtained from these fungi.

Attempts to isolate penicillin were made, but lack of appreciation of its potentialities and the difficulty of preparing enough for experiments caused it to be put aside as a curiosity, although Fleming used it in his laboratory as a method of differentiating bacterial cultures throughout the 1930's.

In 1939, principally as an academic exercise, Chain and Florey undertook an investigation of antibacterial substances produced by micro-organisms (*i.e.* antibiotics). They prepared penicillin, discovered its *systemic* as opposed to local chemotherapeutic power against experimental infections in mice and confirmed its remarkable lack of toxicity.

The importance of this discovery for a nation at war was obvious to these workers but the time, July 1940, was unfortunate, for Britain was being bombed with increasing vigour. It was necessary to manufacture penicillin in the Oxford University Pathology Laboratory where enough was made to start a small clinical trial in 1941. The results were good and it was clear that penicillin might have military significance, but because of the war large-scale production in Britain was not possible. The U.S.A. was still at peace, so arrangements were made for the production of penicillin there. Ample supplies were available to treat casualties in the latter part of the war.

Since 1939 large programmes of screening fungi, actinomycetes and bacteria for antibiotic production have been in progress. The first success was the isolation of streptomycin from a soil organism and this has been followed by the tetracyclines, erythromycin and others. Simultaneously there have been developments in antituberculous agents and in the therapy of many tropical diseases, including malaria, leprosy and amœbiasis.

The natural history of common infections is nowadays rarely seen because chemotherapy is generally given. Perhaps as a consequence of this the danger of some infections, if untreated, has become exaggerated. Suspicion is growing that chemotherapy does not alter the course of all diseases as dramatically as is sometimes assumed. The routine use of chemotherapy in mild cases of boils, endemic sore throat, chronic bronchitis, and whooping-cough is of particularly doubtful merit.

Classification of Chemotherapeutic Agents Used Against Bacteria

The term antimicrobial is used in this book to mean all chemotherapeutic agents used against micro-organisms.

An antibiotic is a substance which is synthesised by one organism and is toxic to other organisms.*

---

* Gale, E. F. (1960). *Brit. med. Bull.*, **16**, 11.

Sulphonamides, isoniazid and para-aminosalicylic acid are therefore *not* antibiotics; they are synthetic antimicrobials.

Antibacterial chemotherapeutic agents may be divided into two groups, those which act primarily by stopping bacterial growth and those which act primarily by killing the bacteria:—

Primarily Bacteriostatic	Primarily Bactericidal
sulphonamides	penicillin
tetracyclines	streptomycin
erythromycin	neomycin
novobiocin	polymyxin
chloramphenicol	
para-aminosalicylic acid	

isoniazid can be included in either group depending on the concentration and temperature.

Most bacteriostatic drugs become bactericidal at very high concentration. The classification has clinical relevance because combinations of chemotherapeutic agents may be synergistic or antagonistic depending on various factors about which little is known; see Combinations of Antimicrobial Drugs, p. 26. When a bacteriostatic drug is used the phagocytic defence mechanism of the body is relied upon to destroy the organisms whose multiplication has been arrested by the drug, so that in the treatment of carriers, where there is no such defence reaction, these drugs cannot be expected to succeed. In cases of agranulocytosis this defence mechanism is greatly impaired and so chemoprophylaxis should be undertaken with a bactericidal drug; penicillin is usually given in practice.

Use and Choice of Antimicrobial Drugs

When deciding on the choice of an antimicrobial, infections fall into two main classes (*6*):—

In the first, choice of antimicrobial follows automatically from the clinical diagnosis because the causative organism is always the same and is always sensitive to the same drug: some hæmolytic streptococcal infections (scarlatina, classical erysipelas), syphilis, typhus, plague, malaria, amœbiasis, leprosy.

In the second, choice of antimicrobial should be based, whenever possible, on bacteriological identification and sensitivity tests because:—

a. The infecting organism is not identified by the clinical diagnosis, for instance, bronchopneumonia, empyema, meningitis, urinary tract infection.

b. The infecting organism is identified by the clinical diagnosis, but no assumption can be made as to its sensitivity to any one antimicrobial, for instance, carbuncle, tuberculosis.

Although bacteriological sensitivity tests are ordinarily a reliable guide to antimicrobial therapy there are exceptional cases. *In vitro* tests occasionally do not parallel *in vivo* sensitivity. This occurs even with the notorious penicillin-resistant staphylococci. Where tests indicate that the organism is very sensitive to a drug, that drug should be used provided the patient is not allergic to it. Where tests show general resistance to drugs or where the apparent drug of choice fails after adequate trial it is worth trying a drug to which the bacteriologist has found the organism less sensitive or even quite resistant. It is always possible that the organism isolated by the bacteriologist is not the prime cause of the disease.

In infections in either sub-division of the second group above there are a number of possible courses of action:—

When bacteriological services are not available at all it may be necessary to choose antimicrobial drugs which cover the maximum range of organisms. Since penicillin is active principally against Gram-positive organisms (and Gram-negative cocci) and streptomycin against Gram-negative organisms (and Gram-positive cocci) a combination of these two drugs might well be the best treatment for a severe infection. A less severe infection might be treated by a single broad-spectrum antibiotic, such as tetracycline, which is effective against a range of Gram-positive and Gram-negative organisms, or by penicillin alone. Treatment should be changed only after adequate trial, usually three days, for over-hasty alterations will only cause confusion and tend to produce resistant organisms. Lack of bacteriological assistance is not an excuse for indiscriminate polypharmacy.

When bacteriological services are available but treatment cannot be delayed it is obviously necessary to act as if they are absent, except that any appropriate specimens (blood, pus, urine, sputum, cerebrospinal fluid) *must* be taken for bacteriological examination before administering any antimicrobial, so that appropriate modification of treatment can be made later if necessary in the light of the sensitivity tests.

When bacteriological services are available but treatment can only be delayed until simple staining tests have been done, the antimicrobial will be selected on the knowledge that the organism is a Gram-positive or a Gram-negative coccus or bacillus. It is therefore necessary to know the approximate range of antimicrobial drugs over organisms so classified (see table, p. 23).

Antimicrobials are usually active against the following organisms:—

Penicillin	Gram-positive and Gram-negative cocci. Some Gram-positive bacilli (C. diphtheria, clostridia, and B. anthracis) Spirochætes
Streptomycin	Gram-negative bacilli Gram-positive cocci Myco. tuberculosis
Tetracyclines	Gram-positive and Gram-negative cocci and bacilli (excluding clostridia) Rickettsiæ Spirochætes E. histolytica
Erythromycin	Similar to penicillin
Sulphonamides	Gram-positive and Gram-negative cocci Gram-negative bacilli

The Gram-staining Properties of some Pathogenic Bacteria

Gram-positive organisms	*Gram-negative organisms*
Streptococcus pyogenes	Neisseriæ (both gonorrhϾ and meningitidis)
Strept. pneumoniæ (pneumococcus)	Escherichia coli
Staphylococci	Salmonellæ
Corynebacteria	Shigellæ
Clostridia	Pseudomonas pyocyanea
Bacillus anthracis	Klebsiella pneumoniæ (Friedlander's bacillus)
Erysipelothrix rhusiopathiæ	Proteus
	Aerobacter aerogenes
	Hæmophili
	Brucellæ
	Vibrio choleræ
	Pasteurellæ

Some organisms are invariably sensitive to certain antimicrobials when they occur in previously untreated patients. Temporary resistance, readily reverting to sensitivity, may occasionally occur in some organisms (hæmophilus, streptococcus) in some patients (*e.g.* chronic bronchitics) taking antimicrobials over long periods. The following list gives organisms invariably sensitive to certain antimicrobials subject to the above qualification.

Streptococcus pyogenes (Group A)	penicillin
Streptococcus pneumoniæ (pneumococcus)	penicillin
Hæmophilus influenzæ and parainfluenzæ	tetracyclines and chloramphenicol
Pseudomonas pyocyaneæ	polymyxin
Neisseria meningitidis	sulphonamides and penicillin
Treponema pallidum	penicillin

When bacteriological services are available and treatment may reasonably be delayed for up to 48 hours, then the antimicrobial drug may be chosen with knowledge of the sensitivity of the organism to the various agents. This course should be followed whenever possible because it gives the best results.

Bacterial Resistance

Bacterial resistance to antimicrobials is a matter of great importance; if sensitive strains are supplanted by resistant ones, then a valuable drug may become useless. So far new discoveries have just kept pace with development of resistance, but already it is sometimes necessary to use the more toxic antimicrobials such as polymyxin, and there are no grounds for assuming that new drug development will always outrun resistance.

The seriousness of the position is shown in the table, p. 25. The total number of staphylococcal infections in a 350-bed hospital in the U.S.A., occurring in patients before admission, during their stay and within 60 days of discharge, is given. It is evident that staphylococcal infections acquired casually are not very serious, but that those acquired in hospital are extremely grave. This is attributed to the fact that in hospitals these organisms are commonly resistant to a wide range of antimicrobials in addition to the fact that patients are already ill. If it is assumed that infections occurring within 60 days of leaving hospital result from the stay in hospital, which seems likely in view of the pattern of antimicrobial resistance, then the incidence of staphylococcal infection, if maintained for a year, is nearly equal to the annual incidence of poliomyelitis in the state of Washington, U.S.A., prior to 1956, *i.e.* before active immunisation was available, and the death rate of the staphylococcal infections is much higher.

Incidence of Staphylococcal Infection in a 350-bed Hospital in the U.S.A. During 3½ Months.*

Time infection occurred	*No. of infections*	*% of infections sensitive to all antibiotics tested*†	*Deaths*
Before admission . .	57	40	2
During stay in hospital	100	3	21
Within 60 days of leaving hospital . .	32	3	1

The problem of bacterial resistance is complex, for some organisms never become resistant to certain antimicrobials (see p. 24) whereas others readily do so. For example, pneumococci and Streptococcus pyogenes never develop penicillin resistance whereas staphylococci do so with alacrity. The meningococcus never becomes resistant to sulphonamides, the gonococcus readily does so.

It is certain that inadequate dosage, in amount or duration, of antimicrobial drugs can promote the selection of resistant strains, and that extensive spread of resistant organisms can be delayed or prevented by proper use of drugs, including the use of combinations (see next page).

The potential seriousness of the problem can be realised when it is remembered that it was largely for its activity against staphylococci that penicillin was acclaimed at its introduction and that now hospital staphylococci are noted for their immunity to the drug. It has been reported (*8*, *9*) that amongst the patients of a general hospital the spread of resistant staphylococci was very rapid (see next page). Of the strains isolated late in 1951 nearly 20% were resistant to the tetracyclines. 54·5% of the staff had positive nasal swabs and 88% of the staphylococci isolated were penicillin resistant.

Gonococci rapidly became sulphonamide resistant. Within ten years of the introduction of sulphonamides the incidence of resistant strains had risen from less than 30% to over 70%, but fortunately by this time the efficacy of penicillin had been established.

Bacterial resistance may be of two kinds, natural, in which the metab-

---

* Data from Wysham, D. N., and Kirby, W. M. M. (1957). *J. Amer. med. Ass.* **164**, 1733.

† Tetracycline, chloramphenicol, streptomycin, penicillin, erythromycin, bacitracin.

INCREASE OF ANTIMICROBIAL-RESISTANT STAPHYLOCOCCI

Year	*Source of staphylococci*	*Percentage of staphylococci resistant to:*	
		penicillin	*streptomycin*
1950	outpatients	24·6	1·1
	inpatients	53·4	14·0
1951	outpatients	36·3	10·8
	inpatients	64·7	27·6

olism of the organism is unaffected by the drug at any time, or acquired. Acquired resistance develops following the exposure of the organism to the drug. It is probably largely due to spontaneous mutation, for there is considerable biological variation in the sensitivity of any strain of bacteria to an antimicrobial. The growth of the resistant mutant is then promoted by lack of competition from the sensitive organisms which have been inhibited. Also bacteria may become adapted to the antimicrobial drug and develop alternative metabolic pathways. It may be that highly resistant strains develop by mutation and slight increases of resistance are the result of adaptation.

Combinations of Antimicrobial Drugs (*24*)

When treating a severe infection or one that is relatively insensitive to antimicrobials, thought is necessary before adding one or two more drugs in the hope of ensuring success. Although little enough is known of the mechanisms by which drugs interfere with bacterial metabolism, there is no doubt that some combinations of antimicrobials, both *in vitro* and *in vivo*, are less effective than one of the drugs used alone. Some bactericidal drugs act most effectively against rapidly dividing organisms and so it is not surprising that concurrent administration of a bacteriostatic drug has been found to protect the organisms rather than to hasten their death. Clinical evidence of such antagonism between drugs is difficult to obtain, but an apparently unimpeachable example has been reported (*10*). Considering that the prognosis of pneumococcal meningitis was improved by the advent of sulphonamides and further by combining penicillin with them, it seemed, in 1951, not unreasonable to hope that the substitution of chlortetracycline for the sulphonamides might still further reduce the death rate.

Alternate cases of pneumococcal meningitis were treated with penicillin and with penicillin plus chlortetracycline. It soon became clear that the patients receiving the two drugs were faring worse than those receiving penicillin alone. The death rate amongst the combined therapy group was 79% and amongst the penicillin group 30%. Patients in the penicillin group who recovered did so more rapidly than those in the combined group. Careful analysis of the groups did not reveal any more likely cause for the difference than the mutual antagonism of penicillin and chlortetracycline.

There is small likelihood of such florid examples appearing often, for any antagonism of antimicrobials tends to be obscured whenever a large excess of one of the drugs is present and this is commonly the case in clinical practice. It has been pointed out (*11*) that the low concentrations of drugs at the site of infection in pneumococcal meningitis were well suited to the demonstration of antagonism. However it would be unwise to presume on the unlikelihood of antagonism and make it an excuse for routine polypharmacy.

Unfortunately it is not possible to state which combinations are synergistic, antagonistic or indifferent as the effects vary according to the organism and the relative concentrations of the drugs. Nor are there simple laboratory tests to reveal effective combinations, for there are too many variable factors, pH of media, duration of action, and initial antagonism followed by synergism being amongst them (*16*).

However, some provisional rules have been formulated (*11*) and these may be accepted until more is known.

Primarily Bactericidal Drugs (group 1), penicillin, streptomycin, neomycin are frequently synergistic to each other, sometimes indifferent, but never antagonistic. They are often used together successfully.

Primarily Bacteriostatic Drugs (group 2), tetracyclines, chloramphenicol, sulphonamides, are neither synergistic nor antagonistic to each other but additive effects may occur which could probably also be obtained by giving a larger dose of one of the drugs.

When a drug of group 1 and group 2 are used together the effects are not certainly predictable. If the organism is highly sensitive to the group 1 drug, antagonism may occur. If the organism is rather resistant to the group 1 drug, synergism may occur. Combinations are also used to prevent emergence of resistant bacteria in tuberculosis, staphylococcal and some urinary tract infections.

The Masking of Infections

The masking of infections by chemotherapy is an important possibility. The risk cannot be entirely avoided but it can be minimised by intelligent use of antimicrobials. For example, a course of penicillin adequate to cure gonorrhœa may merely prevent clinical evidence of syphilis, contracted simultaneously, from appearing until an advanced stage is reached. Casual use of streptomycin in undiagnosed pyrexia may result in delay in diagnosing tuberculosis and the development of resistant organisms.

Nutritional Deficiencies (*20*)

The question of the development of nutritional deficiencies due to prolonged antimicrobial therapy preventing bacterial synthesis of vitamins in the intestine is a vexed one. In animal experiments deficiency of vitamin B complex and of vitamin K have been induced but conclusive evidence of their occurrence in man is lacking. It would obviously be wise to administer vitamin B complex to patients in whom any symptoms similar to deficiency of this group of vitamins occur. Vitamin K deficiency may occur in any case of severe intestinal hurry, irrespective of the presence or absence of antimicrobial drugs.

Superinfection

When any antimicrobial drug is used there is an alteration in the bacterial flora of the patient, which varies according to the drug used. Often this causes no ill-effects, but sometimes a drug-resistant organism proliferates and causes disease which can be serious and even fatal. This complication, superinfection, which may be due to bacteria, yeasts or fungi, has been found to be less rare than was once supposed (*13*). In a study of over 3,000 patients treated with antimicrobials 2% developed superinfection. The organs involved were most frequently those affected by the primary disease and superinfection occurred most commonly on the fourth day of chemotherapy. It was concluded that those most liable to superinfection were patients less than three years old, those with middle ear and lower respiratory tract infections and patients undergoing treatment with broad-spectrum drugs or drug combinations.

Superinfection is often difficult to treat, and since the complication is by no means rare, it is clear that routine chemoprophylaxis of bacterial infections in usually non-serious conditions, *e.g.* measles, is not always in the interest of the patient.

Chemoprophylaxis of Bacterial Infections by Antimicrobials (*12, 13, 23, 25*)

It is sometimes assumed that what a drug can cure it can also prevent, but this is not necessarily so.

Experience has shown that long-term chemoprophylaxis of streptococcal infections in patients who have had acute rheumatism can be achieved by doses of antimicrobials that would be inadequate to treat established infection. Short-term chemoprophylaxis in epidemics of bacterial dysentery, meningococcal meningitis and sterilisation of the large bowel before surgery are also effective. The organisms causing two of these diseases (meningitis and rheumatic fever) are always the same and are always sensitive to penicillin, and in the case of the meningococcus to sulphonamides also. But the efficacy of antimicrobials in preventing pneumonia, urinary infection or wound sepsis following "clean" surgery is much less certain. Evidence is accumulating that attempts at chemoprophylaxis that are not aimed at a particular organism whose sensitivity is known are liable to be not only ineffective but actually to increase the liability to infection. It is no solution to give four or even five drugs, as has been done in an attempt to cover all the likely organisms. There is evidence that chemoprophylaxis of pneumonia in unconscious patients, of bacterial complications of measles, of postoperative infection in "clean" surgery, and of infection in infants born after prolonged labour actually promotes what it is intended to prevent. The same applies to the treatment of mild uncomplicated respiratory infections in children when the leucocyte count is less than 10,000/cmm.

Further controlled studies are needed to evaluate chemoprophylaxis of bacterial infections. It may well be that it is usually better to await complications and then to treat them vigorously, than to try to prevent them.

General Principles of Chemotherapy

The following notes apply to most patients for whom chemotherapy is being considered:—

1. To decide whether chemotherapy is really necessary.

As a general rule, to which there are exceptions, acute infections require chemotherapy whilst chronic infections do not. Chronic abscess, empyema or osteomyelitis for example, respond poorly, although chemotherapeutic cover is essential if surgery is undertaken, in order to avoid a flare-up of infection or its dissemination, due to the breaking down of tissue barriers.

2. To choose the drug on clinical or bacteriological grounds as described above.

3. To administer the drug in full dose having regard to the nature of the organism, its accessibility to the drug and the severity of the infection. An initial loading dose is often desirable.

4. To ensure not only that the total dose is adequate but that it is given at the proper intervals and by the best route or routes. Inadequate dosage may lead to the development of bacterial resistance.

5. To ensure that therapy, once embarked on, is not changed without

the best of reasons until an adequate time for a therapeutic response has elapsed, usually three days in acute infections.

6. If apparent cure is achieved the drug should be continued for about three days further to avoid relapse. There are many exceptions to this, such as typhoid fever, tuberculosis and bacterial endocarditis, in which it is known that relapse is possible long after apparent clinical cure and so the drugs are continued for a time determined by experience.

7. It is abuse of antimicrobials to use them merely as antipyretics. This causes diagnostic confusion, may fail to cure the patient and can even succeed in killing him. Unless a pyrexia is found to be undiagnosable, or is immediately life-endangering, antimicrobials should be withheld until the illness is diagnosed or the patient recovers spontaneously.

8. Two or more antimicrobials should not be used simultaneously without good reason, for mutual antagonism, though rare, can occur.

9. Test of cure. In some infections bacteriological proof of cure is desirable because disappearance of symptoms and signs occurs before the organisms are eradicated, *e.g.* in urinary infections. Bacteriological examination must be done, of course, after the withdrawal of chemotherapy.

10. Measurement of blood levels of antimicrobials is seldom needed, but is essential if there is renal damage and toxic drugs which are excreted by the kidney are used. This is especially likely to happen in the treatment of renal tuberculosis when the first dose or two of streptomycin may give adequate blood levels lasting for days.

11. Carriers need to be treated with bactericidal drugs, for bacteriostatic drugs do not cure, but very large doses of drugs classified as bacteriostatic can be bactericidal.

INDIVIDUAL ANTIMICROBIALS

Sulphonamides

The first preparations (1935) were linked to dyes (Prontosil Rubrum and Album) but it was soon discovered that it was the sulphonamide that had the antibacterial effect and that the dye was unnecessary. One of the first definitive clinical trials was done in 1936 on hæmolytic streptococcal puerperal infections (7). In the five preceding years the mortality rate from this infection in hospital had averaged 23%. From January 1936, when the sulphonamide treatment was begun, to August, the mortality was 4·7%. This fall was so dramatic that it was unnecessary to delay publication of the results until treatment had continued for a full year. The authors admitted that the design of their clinical trial did not exclude as possible explanations of the result a spontaneous alteration in bacterial virulence or, more remotely, the chance admission to hospital of only mild cases in 1936. They discussed these possibilities and found it "difficult to resist the conclusion that the treatment has profoundly modified the course of the infection". This conclusion was soon amply confirmed.

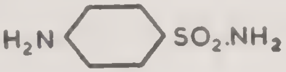
Nowadays it would be considered essential to avoid the undoubted hazard of relying on previous mortality figures for infections, by having two groups of patients treated concurrently and allotted randomly to old and new treatments.

In 1938 sulphapyridine, widely known as M. & B. (May & Baker) 693, was introduced and now there is a surfeit of sulphonamides from which to choose.

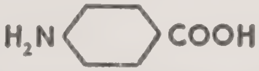
Mode of Action of Sulphonamides

A fairly detailed account is given because sulphonamides illustrate well the important pharmacological principle of competitive inhibition.

Folic (pteroylglutamic) acid is essential for the growth of many bacteria. Para-aminobenzoic acid (PABA) is a precursor of folic acid and sulphonamides are closely related chemically to PABA:—



Sulphanilamide



PABA

Some bacteria (*e.g.* streptococci) are obliged to synthesise their own folic acid from PABA. The hypothesis is that in these bacteria sulphonamides compete with PABA in this metabolic process but that their slightly different chemical structure prevents the bacteria from completing the synthesis to folic acid. As a result the bacteria are deprived of folic acid and cease to multiply. Sulphonamides are therefore primarily bacteriostatic.

This hypothesis is supported by the following facts:—

1. PABA added to a culture medium antagonises the bacteriostatic effect of sulphonamides.

2. Organisms which are sensitive to sulphonamides are those obliged to synthesise their own folic acid.

3. Organisms which do not require folic acid or which can utilise preformed folic acid are insensitive to sulphonamides.

4. Man does not synthesise folic acid inside the body and his cells are immune from this metabolic effect of sulphonamides.

Absorption and Metabolism of Sulphonamides

It is convenient to divide sulphonamides into two main groups according to how well they are absorbed from the intestine.

WELL ABSORBED: sulphadiazine; sulphadimidine (Sulphamezathine); sulphamerazine; sulphafurazole (Gantrisin); sulphasomidine (Elkosin); sulphamethoxypyridazine (Lederkyn); sulphaphenazole (Orisulf).

POORLY ABSORBED: phthalylsulphathiazole (Sulfathalidine); succinylsulphathiazole (Sulfasuxidine); sulphaguanidine (a substantial proportion is absorbed).

In addition there are sulphonamides which, though formerly much used orally, are now used for (*a*) local application to wounds (but not to the skin): sulphanilamide; sulphathiazole; and (*b*) for local application to mucous membranes: sulphacetamide (Albucid).

The following data apply principally to the "well absorbed" group. In practice it is only necessary to use one member of each group.

Absorption after oral administration is fairly rapid and complete from the small intestine. There is insignificant difference in blood levels if the drugs are taken on an empty or on a full stomach.

Distribution is throughout the body water. The sulphonamides get into the cerebrospinal fluid fairly well, especially if the meninges are inflamed, but sulphadiazine gives the highest C.S.F. levels and is the drug of choice in meningitis. 50 to 70% of the sulphonamide in the blood is bound to plasma proteins and so temporarily inactive against bacteria.

Metabolism and Excretion. Sulphonamides are acetylated in the body. Unfortunately the acetylated form is no longer antibacterial but remains toxic. About half the sulphonamide is excreted by the kidney in the free form and half as the acetyl derivative, which is about as insoluble as the parent compound, but this varies in detail from compound to compound. Precipitation of crystals in the urinary tract may occur, causing renal colic, hæmaturia, oliguria and even anuria and death. This risk can be reduced by:—

a. Ensuring a urinary volume of at least two litres a day, which may be difficult in a sick person.

b. Making the urine alkaline, thus increasing the solubility of both the sulphonamide and its acetyl derivative.

The concentration of sulphonamides in the urine is greater than that in the blood, since they pass across the glomerulus and relatively little is reabsorbed by the tubules. Excretion is rapid and the daily intake, distributed throughout the body, is concentrated into about two litres of urine per day. Thus urinary infections may be treated with lower doses than systemic infections, with correspondingly less risk of toxicity.

Renal insufficiency leads to higher sulphonamide blood levels and so enhances toxicity, therefore sulphonamides are more dangerous in patients with a raised blood urea and it may be necessary to control dosage by measuring blood levels repeatedly.

Toxic Effects of Sulphonamides

The less serious effects include malaise, headache, nausea or vomiting, mental depression and rarely cyanosis, which latter is due partly to a harmless metabolic product and partly to methæmoglobinæmia. These may all be transient and are not necessarily indications for stopping the drug.

Serious toxic effects include:—

CRYSTALLURIA, which may progress to anuria (*18*).
HYPERSENSITIVITY REACTIONS of many kinds.
DIARRHŒA, occasionally with superinfection.

When any of these occur the drug should be stopped at once, although a mild crystalluria can be reversed by prompt treatment.

Crystalluria may be symptomless if very mild, but may cause renal pain, hæmaturia, oliguria and eventually anuria. If detected before anuria develops, fluids should be given in large amounts and the urine made alkaline with potassium or sodium citrate by mouth or sodium bicarbonate, by mouth or i.v. according to the state of the patient. The reaction of the urine should be tested to ensure that enough alkali is being given and the sulphonamide should be changed for another chemotherapeutic agent.

Anuria due to crystals must be distinguished from that due to lower nephron nephrosis. A surgeon should be consulted in the former case because ureteric catheterisation or nephrostomy may be necessary, otherwise the anuria is treated in the usual way.

Hypersensitivity reactions due to sulphonamides are not very common but may include drug rash, drug fever, lower nephron nephrosis, hepatitis, agranulocytosis, purpura, aplastic anæmia, hæmolysis, peripheral neuritis, a serum-sickness-like syndrome and polyarteritis nodosa. If any of these allergic toxic effects occur the patient should never again take a sulphonamide, and should be warned accordingly.

Diarrhœa sometimes results from alteration of the intestinal flora. This is most likely to occur with the poorly absorbed sulphonamides. The main danger is that superinfection may occur. The B group of vitamins may be given but may do no good.

Uses of Sulphonamides

Sulphonamides are chiefly used in the treatment of urinary infections, meningococcal meningitis and bacillary dysentery. In most other diseases they have been replaced by the less toxic antibiotics but may still be lifesaving in infections due to antibiotic-resistant organisms. Sulphonamides are sometimes used for prophylaxis of streptococcal throat infections in rheumatic patients, of recurrent urinary infections and of dysentery and meningitis during epidemics.

The principal organisms against which sulphonamides are used are: Streptococcus pyogenes (hæmolytic streptococci), Streptococcus pneumoniæ (pneumococcus), Neisseria meningitidis, Escherichia coli and the Shigellæ. The poorly absorbed members are used solely for infections confined to the bowel.

Bacterial Resistance to Sulphonamides occurs to the whole group, not merely to one sulphonamide. The gonococcus rapidly, but the meningococcus never, becomes sulphonamide resistant.

Sulphonamide Inhibitors occur in pus and may be a cause of failure of therapy when laboratory tests show sensitivity.

Administration and Dosage of Sulphonamides

ORAL. Tablets (0·5 G.) may be crushed; this is more easily done in water. Flavoured suspensions are available for children.

In systemic infections a "loading dose" is given to raise the blood level to therapeutic height as rapidly as possible and then regular maintenance doses are given to keep it there until the temperature has been normal for two or three days. The dose of the sulphonamide may then be halved for a further two or three days, except in the most severe infections. If a good response is not achieved in three days an antibiotic should generally be substituted for the sulphonamide. Treatment should seldom exceed a week or a total of 30 G., because after this the likelihood of allergic toxic effects increases rapidly.

Unless an infection is a threat to life it is sometimes permissible to omit one dose of sulphonamide in the night if the patient is asleep, since it is now known that the importance of maintaining blood levels continuously at bacteriostatic levels is not as great as was once thought; sleep may be more valuable to the patient than drugs. Drug levels in tissues do not fall, or rise, as rapidly as does the concentration in the blood.

Sulphadiazine is a good general-purpose sulphonamide for systemic use, it is the drug of choice when penetration into the cerebrospinal fluid is required. The loading dose is 3 to 5 G., followed by 1 to 1·5 G., 4-hourly. In urinary infections 0·5 G. 6-hourly is usually sufficient without a loading dose.

Sulphadimidine (Sulphamezathine) is a good general-purpose sulphonamide for systemic use, the dose is the same as that of sulphadiazine.

Sulphamerazine is more slowly excreted than the above two and so similar doses can be taken about half as often. It is rather insoluble, and so prone to crystallise in the urine, and is obsolete for this reason (28).

Sulphafurazole (Gantrisin) and **Sulphasomidine** (Elkosin) are comparatively new drugs. They and their acetyl derivatives are more soluble than other sulphonamides and are therefore safer in dehydrated patients or in those unable or unwilling to drink much water. Dosage is as for sulphadiazine.

Sulphamethoxypyridazine (Lederkyn) is well absorbed but slowly excreted. The initial dose is 1 to 2 G. followed by 0·5 G. once a day. Rashes may be more common than with other sulphonamides (*28*).

Sulphaphenazole (Orisulf) is an alternative to sulphamethoxypyridazine.

Phthalylsulphathiazole (Sulfathalidine) is used as an intestinal antiseptic before bowel surgery, sulphathiazole is released from it by bacterial hydrolysis in the colon. The dose is as for sulphadiazine. Although less than 10% is absorbed systemic toxic effects can occur. Liquid paraffin interferes with its action. Constipation may occur and is best relieved by enemas since purgatives are liable to initiate a brisk diarrhœa when used in a patient with abnormal bowel flora.

Succinylsulphathiazole (Sulfasuxidine) has properties similar to phthalylsulphathiazole and acts in the same way. Constipation is uncommon; small semi-fluid stools are usual. The dose, 2 G. 4-hourly, and especially the loading dose, 10 G., is inconveniently large.

Sulphaguanidine is partially absorbed. It is toxic, often ineffective, and is obsolete.

Sulphanilamide and Sulphathiazole are now considered too toxic for systemic use. They are more soluble than other sulphonamides and are sometimes used on wounds, but should be kept off skin.

Sulphasalazine (salicylazosulphapyridine, Salazopyrin) is advocated in chronic ulcerative colitis in doses of 0·5 to 1 G., 4 to 6-hourly, but toxic effects are common and this drug may have no special advantage. Claims that it has a qualitatively different therapeutic effect have not been substantiated.

Sulphacetamide provides a soluble sodium salt which is neutral in reaction, in contrast to the others which are strongly alkaline. It is therefore used locally on mucous membranes, *e.g.* for conjunctivitis. It is also satisfactory for systemic use.

Sulphonamide Mixtures (*15*) are used in an attempt to avoid renal damage by taking advantage of the fact that the solubility of each sulphonamide is independent of the others. Thus, if the urine is saturated with sulphadiazine it is still capable of dissolving sulphadimidine almost up to the saturation limit and then yet another sulphonamide and so on. Thus if one-third of the normal dose of each of three sulphonamides is mixed the chance of renal toxic effects should be much reduced. Unfortunately the antibacterial effect is not always the same as if one drug were being given at full dosage. Trisulphonamide Tablets contain sulphadiazine, sulphamerazine and sulphathiazole.

In patients with poor renal function or a low urinary output it is probably better to use one of the more soluble sulphonamides, sulphafurazole or sulphasomidine.

Parenteral Sulphonamide preparations of the soluble sodium salts are available, sulphadiazine sodium covers all requirements. The route of choice is intravenous, *very* slowly from a syringe, or better in a saline (*not* blood or plasma) infusion. The dose schedule can be as for oral sulphadiazine, but infusion need not be repeated more often than 8-hourly and should be replaced by oral therapy as soon as possible. The concentration of sulphonamide in the solution to be given should preferably not exceed 2·5 G./100 ml. Parenteral administration is very rarely required except in severe meningitis. Sodium sulphonamide solutions are alkaline and also irritant so they may not be given intrathecally, and i.m. injections are better avoided, but if given, sites must be widely spaced and well away from nerves.

Local Application of Sulphonamides. Ointments and creams should never be used on the skin as they are liable to sensitise and cause dermatitis. A powder of sulphathiazole or sulphanilamide is used on wounds, often mixed with penicillin powder. Mucous membranes seldom become sensitised and 10 or 30% solution of sodium sulphacetamide is used in the eye. (Sulphacetamide Eye-drops, Weak or Strong, B.P.C.)

Penicillin

Penicillin is produced by growing one of the penicillium moulds in deep tanks. According to the variety of the fungus and the composition of the medium either benzylpenicillin (penicillin G) or phenoxymethylpenicillin (penicillin V) results. Various other natural penicillins occur but are of little importance. In the general account which follows, "penicillin" refers to benzylpenicillin. Penicillin is stable if kept quite dry and retains activity for well over a year, solutions keep for 4 days at 4° C.

The first clinical trials of penicillin were done in 1941 on a few patients with severe staphylococcal and streptococcal infections which had not responded to surgery or sulphonamides. Even though the patients were given, by present standards, only tiny amounts of penicillin, the beneficial effects were clear. Large-scale statistical clinical trials were out of the question, indeed the drug was so scarce that the patients' urine was collected and the penicillin extracted and used again.

The isolation of the penicillin nucleus, 6-aminopenicillanic acid, in 1959 made possible the production of further penicillins. Whether these will be superior to the older forms remains to be seen. 6-(α-phenoxypropionamido)penicillanic acid (Broxil) is an example.

The mode of action is perhaps by interference with bacterial cell wall synthesis. It is bactericidal, and most effective against rapidly multiplying organisms.

Absorption and Excretion of Penicillin

Benzylpenicillin is rapidly and completely absorbed after injection and 60% quickly appears unchanged in the urine. Oral administration is rather less reliable, partly because penicillin is destroyed by acid in the stomach and partly because absorption from the intestine is incomplete.

About 20% of the penicillin appearing in the urine is excreted by the renal tubule (the rest comes out in the glomerular filtrate) and it is possible to block this tubular excretion by means of drugs (probenecid) and so to increase the blood levels achieved by a given dose. It is, however, usually simpler, except in small children, to increase the dose of penicillin when higher blood levels are desired. In the first few months of life penicillin excretion is slower than in older children and adults. Although much penicillin is excreted in the urine it is not often used in renal tract infections because few of the responsible organisms are sensitive to it.

Phenoxymethylpenicillin is not destroyed by acid and gives reliable blood levels for four hours after an oral dose, but absorption is incomplete, for only 25% appears unchanged in the urine. It is probably not significantly superior in practice to benzylpenicillin given orally.

Distribution is throughout the body tissues, except bone and the nervous system, but concentrations vary and it is necessary to inject penicillin locally if high concentrations are desired in the cerebrospinal fluid, pericardium, pleura, joints and eye (subconjunctival injection).

Toxic Effects of Penicillin

Toxic effects hardly occur following s.c. or i.m. injection except in patients allergic to penicillin, although a dull pain at the injection site is common. The successful i.m. administration of 100 million units a day has been recorded, but nowadays any patient thought to need such doses would probably be better treated with another antibiotic.

Mild diarrhœa may occur with oral penicillin, due to interference with the normal intestinal flora.

Excessive doses into the subarachnoid space may cause meningeal reactions, or even convulsions, by local irritation.

Penicillin lozenges are of no value in throat infections and are liable to cause soreness of the mouth and tongue. The cause of this symptom is uncertain, but it is important to recognise it, for it has led doctors to intensify the offending treatment.

Allergic Effects (*22*) are common with prolonged courses of treatment and in those who have had penicillin before or who have a history of an allergy, such as asthma or eczema. They are commoner after penicillin in oil or procaine penicillin than after aqueous penicillin. Oral penicillin is less liable to cause allergic reactions than injected penicillin. Local application of penicillin to the skin is especially productive of skin allergy.

The commonest effects are itching rashes which may be eczematous or urticarial. A serum-sickness-like syndrome, asthma, drug fever and polyarteritis nodosa occur. Anaphylactic shock is rare but may be fatal; it is said to be most likely to occur with accidental intravenous injection, but also occurs with oral administration. Anaphylactic shock is more likely if a patient has had a previous serum-sickness-like reaction than if he has had an urticarial reaction.

After a tonsillectomy penicillin was administered to a young man and he developed a rash. It was decided to change the treatment, but due to an oversight the patient's name was not removed from the "penicillin list". The patient told the nurse of his sensitivity to penicillin as she was about to give the next injection, but the nurse relied on the list and proceeded with the injection and the patient died of an anaphylactic reaction. A counsel of perfection would be that all patients should be asked about previous allergy as a routine. The drug must be avoided in those with a positive history.

It is sometimes possible, with antihistaminic cover, to continue to give penicillin to a patient after a minor reaction, such as a rash, has occurred during treatment, but this should only be done in grave conditions like bacterial endocarditis, and even then only where no adequate alternative is available. Doctors and nurses who prepare injections carelessly sometimes sensitise themselves to penicillin. If a serious penicillin hypersensitivity has occurred and it is essential to continue the drug (a very rare event) an attempt may be made to desensitise the patient under cover of an adrenocortical steroid and perhaps an antihistaminic. The initial dose of soluble benzylpenicillin may have to be less than one unit and it can be doubled every six hours. If a reaction occurs it will be necessary to reduce the dose again and increase it more slowly. Numerous alternative schemes have been proposed and they are probably no less satisfactory. It may be possible to withdraw the steroid gradually after reaching therapeutic doses, but if symptoms recur it must be continued. It is also necessary to consider the perhaps unpredictable effect of the steroid on the disease process itself. Every effort should be made to find alternative chemotherapy. No attempt should be made to desensitise healthy people who are known to be sensitive to penicillin, for desensitisation often fails, is dangerous and, if achieved, may not last so that the subject must always continue to avoid penicillin.

Patients who are suspected of being hypersensitive to penicillin may be tested before starting treatment, if the drug cannot be avoided. The reactivity of the skin to penicillin does not accurately reflect the presence or absence of general hypersensitivity. False negatives to skin tests are well recognised but a positive test should be taken as a warning, for false positives are rare. Intradermal tests are more reliable than scratch or patch tests, although a patch test is proper to test for sensitivity caused by dermal use. (0·02 ml. of saline solution containing 500 units of penicillin per ml. is injected intradermally. If a negative response occurs the solution strength is increased to 5,000, and then to 50,000, units per ml. A control injection of the saline must of course be given. The test must be read within 20 minutes. The test solution should be identical with the particular preparation it is intended to use.) Even intradermal tests have resulted in anaphylactic shock.

Penicillin hypersensitivity may disappear spontaneously but cannot be relied on to do so. The kind of hypersensitivity that manifests itself as urticaria is especially likely to disappear over a period of months.

The skin test outlined above will not predict those who will have a delayed serum-sickness type of reaction, but such cases may show a positive local reaction after 48 hours.

This brief account of a most complicated subject should suffice to show that when there is even a suspicion of penicillin hypersensitivity the drug is best totally avoided *and the patient warned.* It must be very rare indeed that adequate alternative chemotherapy is impossible.

Uses of Penicillin

Penicillin is used in a wide range of infections, having largely displaced the relatively toxic sulphonamides. There can be few occasions where the indications for penicillin are absolute.

The principal organisms against which penicillin is used are: Streptococcus pyogenes, Staphylococcus pyogenes (Staph. aureus), Streptococcus pneumoniæ (pneumococcus), the Neisseriæ and Spirochætes. It is usually assumed that bacteria are equally sensitive to all the different forms of penicillin. This is an incorrect assumption,* but it is not yet known if such differences in sensitivity are important clinically.

Bacterial Resistance to penicillin is common in staphylococci and rare in streptococci. Acquired resistance is sometimes associated with an ability to make the enzyme penicillinase. Many bacteria which are naturally resistant to penicillin make this enzyme, *e.g.* E. coli.

Preparations and Dosage of Penicillin

Penicillin is usually still measured in units, being assayed on standard Staph. aureus and Bacillus subtilis cultures. Phenoxymethylpenicillin however is prescribed by weight.

---

* Annotation (1960). *Brit. med. J.* (*i*), 559.

Preparations for Injection

Penicillin Injection, B.N.F., or soluble penicillin, is dry soluble benzylpenicillin which is dissolved in water before deep s.c., or i.m., injection. Absorption after subcutaneous is as good as after intramuscular injection. Effective dosage schedules vary greatly. The farther apart the injections in time, the larger must the doses be. It is obviously important to reduce the number of daily injections to a minimum to save both unpleasantness and labour. A commonly used course is 250,000 units i.m., 6 to 8-hourly, and this will give persistent blood levels which are adequate to deal with most sensitive organisms. Equally good results can generally be obtained by 500,000 to 1,000,000 units (0·5 to 1 mega-unit) 12-hourly, but in the most severe cases, or those in which there is serious doubt of the sensitivity of the organism the more frequent injections are desirable. Much higher doses, 10 to 20 mega-units a day, are used in infections by relatively resistant or inaccessible organisms. There is, however, a tendency for unnecessarily large doses of penicillin to be given on the better-safe-than-sorry principle and this should be recognised and controlled, for there is some evidence, though it is not conclusive, that there is an optimum penicillin level for killing bacteria and that a great excess may even retard the chemotherapeutic effect.

Procaine Benzylpenicillin is given by i.m. injection only. It is a comparatively stable salt and liberates penicillin over 12 to 24 hours according to the dose administered. An average dose would be 1 million units once a day or 600,000 units 12-hourly. There is no general agreement on its place in therapy. It is probably best to use soluble penicillin in the most severe infections, especially at the outset, as procaine penicillin will not give therapeutic blood levels for some hours after injection.

Procaine Benzylpenicillin with Benzylpenicillin Injection is an attempt to combine the advantages of soluble penicillin, rapid absorption and high peak blood level, with that of procaine penicillin, slow absorption with lower but steady blood level. It contains 300,000 units of the procaine salt to 100,000 units of soluble penicillin.

Benzathine Penicillin is a depôt preparation which gives low blood levels lasting from a few days to four weeks, following i.m. injection. It is little used in acute infections because the blood levels are low, but has a place in chemoprophylaxis.

Numerous other "depôt" or "repository" penicillin preparations, e.g. benethamine penicillin, are available, including various salts, penicillin in oils and mixtures of the above.

Oral Preparations

Numerous penicillins are available:—

Phenoxymethylpenicillin (penicillin V) is reliable. The tablets should be kept cool and dry. Phenoxymethylpenicillin is given 4 to 6-hourly in doses of 120 to 240 mg. with or without a loading dose. In very severe infections soluble benzylpenicillin should be given by injection for at least the first few doses, for the risk of malabsorption or vomiting reducing the efficacy of oral treatment is too serious. Special delicious preparations can be obtained with which to tempt children. It is immaterial in what relation to food it is given.

Benzylpenicillin as tablets, 200,000 to 400,000 units 4 to 6-hourly on an empty stomach is about as effective as phenoxymethylpenicillin.

PENICILLIN LOZENGES each contain 1,000 units of penicillin and should be allowed to dissolve in the mouth, not sucked, which takes one or two hours. They are useless for sore throats but are useful for oral infections. If used for more than three days a sore mouth is likely to result.

PENICILLIN INHALATIONS are sometimes used for local lung therapy, particularly in bronchiectasis. 3 to 5 ml. of a solution of soluble benzylpenicillin containing 10 to 20,000 units of penicillin/ml. is delivered as an aerosol from a suitable apparatus about four times a day. Soreness is liable to result if the mouth is not rinsed after each inhalation.

INTRATHECAL ADMINISTRATION is used in some cases of meningitis. 10 to 20,000 units of soluble benzylpenicillin are injected daily; other forms should not be used. Concurrent systemic administration is essential.

INTRAPLEURAL INJECTION of one million units of soluble benzylpenicillin is useful in the treatment of empyema.

Streptomycin

Streptomycin is obtained from Streptomyces griseus which was cultured by Waksman in 1944, from a heavily manured field and also from a chicken's throat, and shown to be active against a range of organisms. It was soon introduced into medicine, for pharmaceutical firms had gained experience in cultivating moulds and the new drug was urgently needed for its activity against Myco. tuberculosis and other penicillin-insensitive organisms. The exact mode of action is uncertain but streptomycin interferes with bacterial metabolism. It is bactericidal.

Absorption from the intestine is negligible and streptomycin is used to destroy intestinal bacteria prior to bowel surgery. For systemic use it is given i.m.

Distribution is throughout the extracellular fluid. It penetrates poorly into the cerebrospinal fluid and the eye, moderately into the pericardium and joints, and readily into the peritoneal cavity. Streptomycin is excreted unchanged by the kidney. If renal function is poor the drug will accumulate and cause serious toxicity with ordinary doses; this must be especially remembered when treating renal tuberculosis in which twice-weekly serum assays are desirable to establish correct dosage.

Toxicity of Streptomycin. Toxicity is marked with high doses and is a serious drawback to the use of streptomycin. The gravest toxic effect is eighth cranial nerve damage which increases directly with the size of the dose and the duration of treatment. With 2 G. a day over half the patients develop symptoms during the fourth week and with 1 G. a day a sixth of the patients develop symptoms during the sixth week of treatment. Vestibular damage predominates and dizziness, headache, nausea, vomiting, nystagmus and ataxia occur at first. The symptoms may then settle down and only be noticeable on sudden movement. After weeks or months recovery takes place but it is often incomplete, especially in the elderly. Caloric tests of vestibular function may enable vestibular damage to be detected before serious symptoms occur. The auditory division of the eighth nerve is less vulnerable but tinnitus followed by deafness can occur and may be permanent. The location of the damage, in the eighth nerve, at the end-organ, neurone or in the central connections has not been settled. Streptomycin should obviously be stopped, if possible, before symptoms of eighth nerve dysfunction occur.

The use of streptomycin to destroy vestibular function (bilaterally) in the treatment of Ménière's syndrome (unilateral), while interesting as applied pharmacology, is hardly therapeutics.

Hypersensitivity reactions to streptomycin occur, particularly rashes and fever with eosinophilia; desensitisation is possible (p. 168). Albuminuria occurs rarely, it is reputed to herald no danger. Vague feelings of paræsthesiæ of the lips, headache, lassitude, dizziness may occur after each injection; they are less common if the patient is kept at rest after an injection, and it has been demonstrated that muscular activity hastens absorption after i.m. injection, so that higher blood levels occur. Pain at the injection site is common.

Dihydrostreptomycin was introduced in an attempt to avoid the vestibular toxic effects of streptomycin, but it was soon found that dihydrostreptomycin was very toxic to the auditory division of the eighth nerve and deafness is liable both to appear and to progress even after administration of the drug has ceased.

A mixture of equal parts of streptomycin and dihydrostreptomycin has been used in attempt to reduce the toxic effects of both drugs. Its efficacy for this is not finally established.

Uses of Streptomycin

Streptomycin is principally effective against: Myco. tuberculosis, E. coli, Proteus vulgaris, Hæmophilus influenzæ, Brucella abortus and Klebsiella pneumoniæ (Friedlander's bacillus).

In urinary infections the urine may be made alkaline as this enhances the antibacterial action and, since bacterial resistance may develop in a matter of hours, heavy doses (1 G., 8-hourly) may be used, but only for three days. Laboratory sensitivity tests should be employed before beginning streptomycin treatment. Failure of, say, a patient with urinary infection to improve within two or three days should lead to withdrawal of the drug unless the organism can be shown to have retained its sensitivity. In the treatment of tuberculosis, streptomycin is always combined with another agent, such as isoniazid and/or PAS, as this delays development of resistance. The drugs probably act at different metabolic sites. Streptomycin should be given daily, as the use of one or two injections a week allows resistant mutants to proliferate. It is especially important to avoid inducing streptomycin resistance as the toxicity of the drug prohibits the use of massive doses to overcome it. Bacteria sometimes develop a dependence on streptomycin but it is not known whether this ever has clinical importance.

Streptomycin Sulphate Injection, B.P. The dry salt should be dissolved in water immediately before use, 3 ml. to 1 G. Ready prepared solutions containing preservative are available. It is given i.m., a usual dose being 1 G. a day as a single dose or 0·5 G. twice a day. Occasionally 3 G. a day is given for two or three days only. Mixtures of equal parts of streptomycin and dihydrostreptomycin (streptoduocin) may be given as above.

Intrathecal Injection is rarely indicated. Streptomycin is irritant to the meninges and neurotoxicity is enhanced by using this route. The dose is 20 to 50 mg. in at least 3 ml. distilled water. Commercial solutions containing preservative should be avoided and a solution freshly prepared on each occasion. Dihydrostreptomycin should never be used in this way.

Oral Streptomycin tablets, 1 G. 6-hourly for three days, may be used prior to bowel surgery.

Application of Streptomycin to the Skin is undesirable as sensitisation is liable to occur. Doctors and nurses who prepare injections carelessly sometimes develop rashes.

Chloramphenicol

Chloramphenicol was obtained by Burkholder in 1947 from a streptomyces found in a soil sample from a mulched field in Venezuela. It was soon made synthetically. Chloramphenicol was the first antibiotic with a wide range of activity over common organisms which was also reliably absorbed from the intestine. It was also dramatically effective against organisms hitherto immune from therapy, salmonellæ and rickettsiæ. Unfortunately its use in trivial infections rapidly became widespread with tragic results for some patients. Chloramphenicol is primarily bacteriostatic.

Absorption of Chloramphenicol from the alimentary tract is almost complete so that alteration of the bowel flora and consequent diarrhœa is rare. Chloramphenicol is largely metabolised by the liver; however, enough is excreted unchanged in the urine for it to be effective in the treatment of urinary infections.

Distribution of Chloramphenicol is approximately even throughout the body but levels in the pleural space and cerebrospinal fluid, in the absence of inflammation, are about half the blood levels. In meningitis the levels in cerebrospinal fluid approximately equal those in the blood.

Toxicity of Chloramphenicol

Gastro-intestinal symptoms are uncommon but yeast superinfection may occur. Rashes are rare. Chloramphenicol had been in clinical use for three years before its most serious toxic effects, blood dyscrasias, were reported. The blood dyscrasia may be thrombocytopenia, granulocytopenia or, worse, aplastic anæmia, any of which may be fatal. Bone marrow damage is more likely to occur after repeated or prolonged or heavy courses of treatment. Although the incidence is low, chloramphenicol should not be used systemically in any case where another antibiotic would serve. Particularly it should not be used "blind" in the treatment of mild diseases, *e.g.* urinary infections, especially as these are often recurrent, and recurrent use of chloramphenicol is especially to be avoided. Laboratory testing of the infecting organism should precede the use of the drug, except in a disease such as typhoid where there is no choice.

Uses of Chloramphenicol

Chloramphenicol has a wide range of activity but is principally used against the salmonellæ, rickettsiæ and Hæmophilus influenzæ, in addition to organisms shown to be resistant to other antibiotics and sensitive to chloramphenicol. It is less effective against Hæmophilus pertussis than a tetracycline.

Casual use of chloramphenicol is deplorable. "A girl of four years had an attack of bronchitis with asthma for which she received 1 G. chloramphenicol daily for four days. Six months later she developed a sore throat, which was treated with a further course of chloramphenicol 1 G. daily for four days. Three days after completing this course a purpuric rash appeared and in spite of blood transfusion she died two weeks later." Aplastic anæmia was found at necropsy.*

* GAIRDNER, D. (1954). *Brit. med. J.*, (*ii*), 1107.

Bacterial Resistance is comparatively unimportant with chloramphenicol.

Chloramphenicol Capsules, B.P., are given orally, 500 mg. 6-hourly (loading dose 1 to 2 G.), until two or three days after fever or symptoms have subsided. Generally a total of 26 G. should not be exceeded and the duration of treatment should be less than 10 days. For children, 100 mg./Kg. daily for seven days has been proposed as a maximum course; a suspension of chloramphenicol palmitate or cinnamate is available for them.

Chloramphenicol succinate may be given i.m. or i.v., 1 G. 6 to 8-hourly, if oral administration is not feasible.

Preparations for ear, eye and skin are available and are widely used because sufficient absorption to cause blood dyscrasia is unlikely by these routes and skin hypersensitivity is not common.

Treatment of Typhoid and Paratyphoid Fevers

The efficacy of chloramphenicol against typhoid fever was first reported in 1948.* Whilst trying the drug against scrub typhus in Malaya so many cases of typhoid fever were seen that it was decided to treat it with chloramphenicol too. Ten cases were treated against eight controls. The results were dramatic, the average duration of fever being reduced from 26 to 3½ days. Since then numerous reports have confirmed the beneficial effects of chloramphenicol in typhoid fever.

The oral dose of chloramphenicol should be high, 750 mg. 6 or 8-hourly until the fever subsides, followed by 500 mg. 6 or 8-hourly for about another 10 days. The general care of the patient, feeding, control of electrolytes and nursing are at least as important as the chemotherapy.

Tetracyclines have some effect in typhoid, but far less than chloramphenicol.

Relapses after chloramphenicol are common if treatment is continued for less than two weeks. Fortunately they nearly always respond to treatment as readily as the initial infection, bacterial resistance being uncommon. Adrenocortical steroids have been advocated in severe cases where there is great "toxæmia" and favourable results have been reported.

In the treatment of typhoid carriers chloramphenicol is valueless, perhaps because there is no inflammation and therefore no mobilisation of the body defences to destroy the organisms prevented from multiplying by the bacteriostatic drug. Oral streptomycin may be useful against intestinal carriers only. Large doses of penicillin may be tried. The position is very unsatisfactory.

Prophylactic active immunisation against typhoid and paratyphoid fever is effective.

* WOODWARD, T. E., *et al.* (1948). *Ann. intern. med.*, **29**, 131.

The Tetracyclines

The group includes: chlortetracycline (Aureomycin) 1948; oxytetracycline (Terramycin) 1950; tetracycline (Achromycin) 1952.

These are all obtained from soil streptomyces, but tetracycline can also be made from either of the others. The differences between the tetracyclines are small, although testing sometimes reveals that an organism is more sensitive to one than to another. Cross-resistance is complete, that is, an organism resistant to one of the tetracyclines is resistant to all. **They are primarily bacteriostatic.**

The tetracyclines are only partially absorbed from the alimentary tract, enough remaining in the intestine to alter the flora and to give rise to troublesome and sometimes dangerous complications. They are distributed throughout the body, but i.v. administration is needed to get high levels in the cerebrospinal fluid. They are excreted, largely unchanged, in the urine and so may be useful in urinary infections.

Toxicity of the Tetracyclines

Heartburn, nausea and vomiting due to gastric irritation, are common. Attempts to reduce this with milk or other food or antacids are permissible provided no aluminium salt is used, for this drastically reduces absorption. Loose bowel motions occur, due to alteration of the bowel flora, and this sometimes proceeds to diarrhœa which may be controlled by Kaolin, or Kaolin and Morphine Mixture, B.P.C. However, the diarrhœa may also be due to serious superinfection with yeasts (monilia), fungi or tetracycline-resistant bacteria, particularly staphylococci. This complication can be fatal. The tetracycline should be withdrawn but substitution of another antibiotic should not be made unless the superinfecting organism is shown to be sensitive to it. In the case of monilia, and perhaps fungi, the use of nystatin may be considered. Withdrawal of the tetracycline as soon as definite diarrhœa occurs is probably the wisest course; spontaneous recovery is then usual. It is said that tetracycline causes fewer alimentary tract side effects than either oxy- or chlortetracycline, but this may not be so. Administration of a purgative to a patient with abnormal bowel flora is risky, as it is liable to precipitate diarrhœa.

Disorders of epithelial surfaces, perhaps partly due to vitamin B complex deficiency and partly to mild superinfection with yeasts or moulds, lead to sore mouth and throat, black hairy tongue, dysphagia and peri-anal soreness. There is some evidence that administration of vitamin B preparations may prevent or arrest alimentary tract symptoms. It is probably wise to give these vitamins routinely if tetracycline therapy is to be prolonged.

Allergic rashes occur.

Uses of the Tetracyclines

The principal organisms against which the tetracyclines are used are: Strept. pyogenes, Staph. pyogenes, Strept. pneumoniæ (pneumococcus), Entamœba histolytica, Brucella abortus, Hæmophilus influenzæ, rickettsiæ such as cause typhus and Q fever, and large viruses such as cause lymphogranuloma and psittacosis. The full range of activity is wider than this. The spectrum of the tetracyclines overlaps that of penicillin and therefore a choice between them must often be made. It is impossible to lay down exact rules, but in general penicillin is used both because it is safer and because the more the newer antibiotics are used the more frequently resistant bacteria will emerge and therefore the smaller will become the reserves of antibiotics for treatment of resistant infections. However, in severe infections treated in the home where frequent injections are impracticable a tetracycline is used, for in such circumstances oral penicillin alone does not yet command complete confidence.

Bacterial Resistance occurs to all the tetracyclines at once, especially amongst staphylococci. There is some cross-resistance with chloramphenicol.

Oral Administration is as tablets or capsules, 250 mg. 6-hourly, with a loading dose of 1 G. In very severe infections 250 mg. may be given 3-hourly, when more is absorbed than if the 6-hourly dose is doubled.

Parenteral Administration is best by intermittent i.v. infusion of tetracycline or oxytetracycline (chlortetracycline is unstable) in 0·9% sodium chloride or 5% dextrose solutions. About 1 G. a day is given in two to four doses. Since strong solutions cause thrombophlebitis, the solution should not contain more than 10 mg./ml. and since too rapid infusion may make the patient feel ill, it should flow at up to 2 ml./min. A slow continuous infusion may be used instead. Injection i.m. is feasible and preparations contain procaine to reduce the pain.

Topical Application is less liable to induce sensitisation than is penicillin. Ointments and solutions are available (but see p. 422).

Demethylchlortetracycline

This gives slightly higher blood levels for a slightly longer time than the other tetracyclines. It is not yet decided whether it is clinically superior.

Erythromycin (1952)

Erythromycin is obtained from a soil streptomyces. It is primarily bacteriostatic. It is well absorbed from the intestine if given in specially coated tablets to protect it from the destructive action of gastric acid. Erythromycin penetrates poorly into the cerebrospinal fluid but moderately into peritoneal and pleural cavities. Excretion is chiefly in the urine.

Toxicity of Erythromycin is low. The bowel flora is altered less than by the tetracyclines, but nausea, vomiting and diarrhœa may occur.

Uses. Erythromycin should be kept in reserve to deal with organisms resistant to other antibiotics. It is the drug of choice against penicillin-resistant staphylococci. Its spectrum is similar to that of penicillin, but it does have some effect against rickettsiæ and large viruses.

Bacterial Resistance to Erythromycin occurs, especially amongst staphylococci, which is why it should be kept as a reserve drug. There is cross-resistance with carbomycin and to some extent with oleando- and spiramycin.

Oral Administration of Erythromycin is by tablet or suspension, 300 to 500 mg. 4 or 6-hourly with a loading dose of 1 G. With suspensions gastric antacids may be used to protect the drug.

Intravenous Administration of Erythromycin is by slow infusion of 300 to 500 mg. or more, of a soluble salt, 8 to 12-hourly. Injection i.m. is undesirable because it is irritant, but may be used. Ointments are available but are probably undesirable (p. 422).

Minor Antibiotics

The antibiotics to be described are included because:—

1. They may be used topically without serious risk of sensitisation.
2. They may be required in the uncommon event of an organism being or becoming resistant to all the antibiotics previously described.
3. They have an antibacterial spectrum extending beyond the antibiotics already described.
4. Their use is limited by their toxic effects.

Bacitracin

In 1943, an antibiotic-producing bacillus was isolated from a compound fracture of the tibia in a 7-year-old girl, Margaret Tracey, during an investigation of the bacterial flora of contaminated accidental wounds. The antibiotic was named after her.

Unfortunately bacitracin is too toxic to the kidney to be used systemically as a routine, but has found a place in topical application to skin and eye. It has a wide spectrum of activity and rarely induces sensitivity or bacterial resistance so that it is preferable to penicillin or sulphonamides for use on the skin. Neomycin, however, has a wider spectrum. Bacitracin is usually applied to skin infections as an ointment once or twice a day.

Being poorly absorbed from the alimentary canal it can be used to reduce the intestinal flora before surgery.

Neomycin

Neomycin was isolated in 1949 from a streptomyces. It is principally used topically and for its antibacterial action in the bowel, from which there is hardly any absorbed, and for which it is preferred above streptomycin because its spectrum is wider. It is often effective against staphylococci, coliform bacilli and Proteus.

Neomycin is best not used systemically because it is toxic to the kidney and eighth cranial nerve, but in infections resistant to other agents it should not be withheld, and, if renal function is good, serious toxicity is unlikely to occur in less than a week. It seldom induces sensitisation when applied to the skin and bacterial resistance is as yet uncommon. There is no cross-resistance with streptomycin. As an intestinal antiseptic 1 G. is given 4-hourly for one or two days. It is the most rapidly effective intestinal antiseptic and is probably the best antibiotic to use in hepatic failure, 4 to 10 G. daily. Parenteral therapy should be by 6-hourly i.m. injections with a maximum of 2 G. in 24 hours.

Neomycin is available as an ointment for skin or eye.

Polymyxin B (1947)

The polymyxins are obtained from a soil bacillus and were discovered simultaneously in three laboratories. Polymyxin B is used because it is least toxic.

Polymyxin B is not significantly absorbed from the alimentary tract and is sometimes used as an intestinal antiseptic. It can be given i.m., and enough is excreted by the kidney for it to be useful in urinary infections. Impaired renal function may lead to cumulation with severe toxicity. It does not enter the cerebrospinal fluid and must be injected intrathecally if used in meningitis.

Polymyxin B is toxic to the nervous system; nausea, dizziness, paræsthesiæ, especially circumorally, ataxia and dysarthria may occur with high doses. It is also toxic to the kidney especially if damage already exists. These effects are reversible. Rashes and drug-fever occur rarely.

The antibacterial spectrum of Polymyxin B is narrow and bacteriological control is desirable. It is used against severe infections which fail to respond to other antibiotics. It is especially useful against Pseudomonas pyocanea and Proteus. Bacterial resistance is not a clinical problem.

The i.m. dose is 60 mg. 4-hourly, dissolved in 0·5 ml. 1% procaine to reduce the pain (1 mg. = 6,000 units approximately). For intrathecal injection, 5 to 10 mg. is given in 1 ml. 0·9% sodium chloride daily for three or four days, then on alternate days.

Polymyxin is used for topical application to eye, ear and skin either alone or mixed with bacitracin and neomycin and is unlikely to sensitise the patient.

Tyrothricin (1939)

Tyrothricin is a mixture of two antibiotics, gramicidin and tyrocidine, made by a bacillus. It was discovered in experiments in which soil was repeatedly inoculated with pathogenic bacteria.

It is too toxic for systemic use, causing hæmolysis and hepatic damage, and so is only used locally, in ointments and solutions. It may induce disorders of smell if used in the nose.

Tyrothricin has a moderately wide spectrum against pyogenic bacteria, diphtheria and ringworm organisms. Both sensitisation of the patient and bacterial resistance are rare.

Viomycin (1954) and Cycloserine (1957)

Viomycin and cycloserine are toxic but may be used against tuberculosis when all else has failed.

Novobiocin (1957)

Novobiocin is an antibiotic which is rarely needed except in the treatment of severe staphylococcal infections, in which it is generally considered desirable to use two drugs. There is no cross-resistance with erythromycin. It is readily absorbed from the alimentary tract and is prone to cause rashes. Staphylococci readily develop resistance to it and it is best kept in reserve for otherwise untreatable infections. It can be given i.v. if necessary. The oral dose is 250 mg. 6-hourly, or twice that in resistant infections.

Nystatin (1955)

Nystatin (named after the New York State Department of Health) is clinically active against yeasts and perhaps moulds, but not against bacteria. It may be needed in patients whose life is endangered by superinfection such as occurs following use of the tetracyclines. It is relatively non-toxic and is poorly absorbed from the alimentary canal, although enough may be absorbed to control urinary moniliasis, for which vesical instillations may also be tried. It may be used locally on yeast infections, for instance oral or vaginal thrush. Injections have not been successful as nystatin is very insoluble and causes pain. For pulmonary moniliasis a suspension of the powder is inhaled from a suitable machine.

Carbomycin (1952)

Carbomycin has an antibacterial spectrum similar to erythromycin, to which it is inferior, and cross-resistance is complete.

Oleandomycin (1957) and Spiramycin (1956)

These substances have limited cross-resistance with erythromycin. They have been advocated for routine use in staphylococcal infections, especially in combination with tetracycline. Their utility when used thus cannot be considered proved.

Vancomycin (1956)

This may be used as a last hope against staphylococci. It must be given i.v.

Griseofulvin (1959)

Griseofulvin (Grisovin) is the first drug to be effective, taken orally, against superficial fungus infections in man. It is produced by a penicillium mould, but has no antibacterial effect.

Griseofulvin was discovered in 1939, but was not introduced into clinical practice until 1958, although it had been used some years earlier to control moulds on vegetables grown in glasshouses. Its great insolubility had seemed a bar to clinical efficacy.

Griseofulvin is effective against all superficial ringworm (dermatophyte) infections. It is taken into keratin, including hair, and exercises its fungistatic effect there. Griseofulvin is especially valuable in ringworm of the nails and hair, for which treatment was previously unpleasant and difficult. Although potentially toxic, griseofulvin, 1 G. a day, has so far only given rise to headache, malaise, gastro-intestinal symptoms and rashes. Depression of the blood leucocyte count occurs, but has not so far proved serious. Griseofulvin should not, however, be used for trivial infections, for these are often amenable to topical applications. Duration of therapy is from weeks to months, depending on the infection. Disease of the nails needs the longer period, and so may hair infection, for griseofulvin does not kill fungus already established, it merely prevents infection of new keratin, so that re-infection will occur if treatment is stopped whilst infected keratin is still on the body. Local hygiene therefore remains important. Treatment must continue for a time after both visual and microscopic evidence of infection has disappeared.

Oral dosage: adults 1 G. daily in two or four doses, reduced to 0·5 G. daily after the first two to three weeks. Children may be given 250 to 500 mg. daily.

The above recommendations may well be modified as experience grows (*26*, *29*).

There are many more antibiotics (kanamycin, ristocetin, amphotericin), and it is to be expected that new examples will continue to be introduced,

LIBRARY
5143
5/4/62

chiefly as alternatives to the established drugs in cases where acquired bacterial resistance occurs, but occasionally extending the scope of chemotherapy to parasites hitherto immune.

GUIDE TO FURTHER READING ON CHEMOTHERAPY AND CHEMOTHERAPEUTIC AGENTS

(1) WORK, T. S., and WORK, E. (1948). The Basis of Chemotherapy. Edinburgh: Oliver & Boyd.

(2) FLOREY, H. W., *et al.* (1949). Antibiotics: A Survey of Penicillin, Streptomycin, and Other Antimicrobial Substances from Fungi, Actinomycetes, Bacteria and Plants. Vols. 1 and 2. London: Oxford University Press.

(3) FLOREY, M. E. The Clinical Application of Antibiotics. Vol. 1, Penicillin (1952). Vol. 2, unpublished. Vol. 3, Chloramphenicol and the Tetracyclines (1957). Vol. 4, Erythromycin etc. (1960). London: Oxford University Press.

(4) FINDLAY, G. M. Recent Advances in Chemotherapy. Vol. 1, 1950. Vol. 2, 1951. Vol. 3 (VALENTINE, F. C. O., and SHOOTER, R. A.), 1954 London: Churchill.

(5) MARQUARDT, M. (1949). Paul Ehrlich. London: Heinemann.

(6) GARROD, L. P. (1955). *In* Discussion on the use and abuse of antibiotics. *Proc. roy. Soc. Med.*, **48**, 355.

(7) COLEBROOK, L., and KENNY, M. (1936). Treatment with prontosil of puerperal infections. *Lancet*, (*ii*), 1319.

(8) ROUNTREE, P. M., BARBOUR, R. H. G., and THOMSON, E. F. (1951). Incidence of penicillin-resistant and streptomycin-resistant staphylococci in a hospital. *Lancet*, (*i*), 435.

(9) ROUNTREE, P. M., and THOMSON, E. F. (1952). Incidence of antibiotic-resistant staphylococci in a hospital. *Lancet*, (*ii*), 262.

(10) LEPPER, M. H., and DOWLING, H. F. (1951). Treatment of pneumococcic meningitis with penicillin compared with penicillin plus aureomycin. Studies including observations on an apparent antagonism between penicillin and aureomycin. *Arch. intern. Med.*, **88**, 489.

(11) JAWETZ, E., and GUNNISON, J. B. (1953). Antibiotic synergism and antagonism: an assessment of the problem. *Pharmacol. Rev.*, **5**, 175.

(12) PETERSDORF, R. G., *et al.* (1957). A study of antibiotic prophylaxis in unconscious patients. *New Engl. J. Med.*, **257**, 1001.

(13) WEINSTEIN, L., GOLDFIELD, M., and CHANG, T. W. (1954). Infections occurring during chemotherapy. *New Engl. J. Med.*, **251**, 247.

(14) HAWKING, F., and LAWRENCE, J. S. (1950). The Sulphonamides. New York: Grune & Stratton.

(15) Annotation (1959). Sulphonamide mixtures. *Brit. med. J.*, (*i*), 40.

(16) Editorial (1957). Antibiotic combinations. *Brit. med. J.*, (*ii*), 1418.

(17) Annotation (1957). Bacteriostatic or bactericidal? *Lancet*, (*ii*), 235.

(18) ARNEIL, G. C. (1958). Twenty-nine children with sulphonamide hæmaturia. *Lancet*, (*i*), 826.

(19) MARSHALL, E. K. (1952). Dosage schedule of chemotherapeutic agents. *Pharmacol. Rev.*, **4**, 85.

(20) JUKES, T. H., and WILLIAMS, W. L. (1953). Nutritional effects of antibiotics. *Pharmacol. Rev.*, **5**, 381.

(21) Umbreit, W. W. (1953). Mechanisms of antibacterial action. *Pharmacol. Rev.*, **5**, 275.
(22) Guthe, T., Idsoe, O., and Willcox, R. R. (1958). Untoward penicillin reactions. *Bull. Wld. Hlth. Org.*, **19**, 427.
(23) Myers, R. S. (1959). The misuse of antibacterials in inguinal herniorrhaphy. *Surg. Gynec. Obstet.*, **108**, 721.
(24) Discussion on synergy in chemotherapy. *Proc. roy. Soc. Med.*, 1956, **49**, 871.
(25) Hardy, M., and Traisman, H. S. (1956). Antibiotics and chemotherapeutic agents in the treatment of uncomplicated respiratory infections in children. *J. Pediat.*, **48**, 146.
(26) Editorial (1960). Griseofulvin. *Lancet*, (*i*), 1175.
(27) Antibiotics in medicine, a symposium. *Brit. med. Bull.*, 1960, part 1.
(28) Newbould, B. B., and Kilpatrick, R. (1960). Long-acting sulphonamides and protein binding. *Lancet*, (*i*), 887.
(29) Russell, B., *et al.* (1960). Chronic ringworm infection of the skin and nails treated with griseofulvin. Report of a therapeutic trial. *Lancet*, (*i*), 1141.

Chapter 4

CHEMOTHERAPY OF INDIVIDUAL DISEASES

SINCE there is commonly more than one antimicrobial which could be used in any disease, the principal infections will now be discussed chiefly from the point of view of choice of drug. Doses are those given in the independent description of each drug except where otherwise stated. It would be repetitious to discuss alternative therapies which might be chosen in the light of bacteriological reports or after failure of the apparent drug of choice. In these cases treatment will follow the general principles discussed in the preceding chapter.

Staphylococcal Infections (*10*)

Staphylococcal infections such as staphylococcal pneumonia, septicæmia, wound or urinary-tract infection, require bacteriological identification of the organism and determination of its drug sensitivity for proper treatment. Staphylococci provide the worst example of the recent serious increase in antimicrobial-resistant strains of organisms. Ordinary doses of penicillin are now very seldom useful in staphylococcal infections acquired in hospital and the tetracycline group is becoming less useful. Most staphylococci in Britain are still sensitive to erythromycin and novobiocin but these should not be used if penicillin or a tetracycline will serve, but should be kept in reserve for as long as possible. The same applies to oleandomycin and spiramycin, which show some cross-resistance with erythromycin, and to chloramphenicol. Sulphonamides are almost never useful in staphylococcal infections even if laboratory tests are favourable, because of the sulphonamide inhibitors present in pus. When all else fails, vancomycin, kanamycin, ristocetin or bacitracin may be needed. Enormous doses of penicillin may be effective even when the staphylococcus appears resistant to it by laboratory tests. Staphylococcal skin infections, boils and carbuncles may require systemic antibiotics.

In the severe pneumonia occurring in influenzal epidemics, which is commonly staphylococcal and often fatal, treatment cannot wait on bacteriological tests. Erythromycin should be given at once (plus chloramphenicol in case it is not staphylococcal) with an adrenocortical steroid for the collapse.

In severe staphylococcal infections it may be best to use two drugs at once, for instance penicillin or erythromycin plus novobiocin, for greater antibacterial effect as well as to prevent development of resistant organisms.

Sore Throats and Streptococcal Infections

Sore Throat may be endemic or epidemic. In the endemic form 50 to 75%, and in an epidemic 100%, may be due to Strept. pyogenes which is invariably sensitive to penicillin. Unfortunately streptococcal sore throats cannot be clinically differentiated from the non-streptococcal with any certainty. Prevention of complications is much more important than relief of the symptoms, which seldom last long.

There is no general agreement whether chemotherapy should be employed in mild endemic sore throat. In these patients the disease usually subsides in a few days, septic complications are uncommon and rheumatic fever rarely follows. It is reasonable to withhold penicillin in these cases unless streptococci are cultured.

Severe endemic sore throat carries a greater likelihood of septic complications, such as otitis media, and should be treated actively with penicillin from the outset, a bacteriological diagnosis being made in addition, if possible.

Epidemic sore throat is almost invariably streptococcal, and the substantial likelihood of both septic complications and rheumatic fever demand early and vigorous penicillin therapy. In a closed community penicillin prophylaxis of unaffected people to stop an epidemic may be considered, for instance phenoxymethylpenicillin 120 mg. by mouth, twice a day, for a period depending on the course of the epidemic, or a single injection of 1·2 million units of benzathine penicillin.

The occurrence of sore throat in any patient who has had rheumatic fever or nephritis is an indication for immediate penicillin therapy.

That penicillin therapy reduces the likelihood of rheumatic fever following streptococcal infection is now accepted, one clinical trial (*3*) in a closed community of young men gave the following result:—

	Number of Patients	
	Penicillin treated	*Controls*
Total number of patients with streptococcal sore throat	978	996
Definite rheumatic fever	2	28
Possible rheumatic fever	3	7

Sulphonamides are less effective against sore throat, do not prevent late complications and may leave a carrier state.

Antibiotic lozenges are ineffective in sore throat and may cause resistant organisms to appear. Antiseptic lozenges and gargles may be comforting to the patient but probably have no influence on the course of the disease.

In Scarlet Fever and Erysipelas the infection is inevitably streptococcal and penicillin should be used even in mild cases to prevent rheumatic fever and nephritis.

Treatment of Tonsillitis is similar to that of epidemic sore throat.

Chemoprophylaxis of Streptococcal Infection should be undertaken in patients who have had an attack of rheumatic fever. It is continued for at least five years, or until aged 18, whichever is the longer period, although some hold that it should continue for life, for histological study of auricular biopsies shows that the cardiac lesions may progress despite absence of clinical activity. Chemoprophylaxis should certainly be continued for life after a second attack of rheumatic fever.

In the rare cases of nephritis in which recurrent hæmaturia occurs after sore throats, chemoprophylaxis may be used. It is sometimes also used in the nephrotic syndrome, as infections may be followed by increased albuminuria.

Ideally, prophylaxis should continue throughout the year, but if the patient is unwilling to submit to the routine, at least the winter months should be covered.

Relatively low doses of penicillin and sulphonamides have been shown to be effective prophylactics, but penicillin is preferable because sulphonamide-resistant Strept. pyogenes (Group A) do occur, although they are uncommon.

Suitable régimes for prophylaxis include: phenoxymethylpenicillin, 60 to 120 mg., or benzylpenicillin, 100,000 to 200,000 units, by mouth once a day, or benzathine penicillin, 1·2 million units i.m. every four to six weeks, or sulphadiazine or sulphadimidine, 0·5 to 1 G. by mouth once a day.

Toxic effects are uncommon. The choice between daily oral or 4 to 6-weekly injections will depend chiefly on convenience to the patient and whether he can be relied on to take daily doses.

Acute Infections of the Middle Ear and Nasal Sinuses commonly respond to penicillin. In children a single big dose may be given i.m. ($\frac{1}{2}$ to 1 million units according to size) if oral administration is impracticable.

Chronic Middle-ear and Sinus Infections may be treated with topical application of antibiotics, such as penicillin, chloramphenicol, polymyxin B, bacitracin, with or without hydrocortisone, combined, if necessary with surgery.

Vincent's Angina, due to a spirochaete and a fusiform bacillus, responds rapidly to penicillin; a single dose of 1 million units i.m. is often enough. Dental treatment may be required to prevent recurrences.

Diphtheria. Antitoxin, 20,000 to 100,000 units, i.m. or i.v. (after a test dose, p. 117) according to the severity of the disease, is given as soon as the diagnosis is even suspected. Erythromycin or penicillin is also used to prevent the production of more toxin by destroying the bacteria. Tyrothricin locally would seem reasonable in addition in cutaneous diphtheria.

Respiratory Infections

Acute Bronchitis. Severe cases require chemotherapy. Penicillin or a tetracycline is usually effective, but if they fail chloramphenicol may have to be used.

Chronic Bronchitis. Continuous antibiotic therapy has been shown to reduce the volume and purulence of the sputum and to prevent acute exacerbations. The bacterial flora is always mixed, but pneumococci and hæmophilus are the pathogenic organisms. Long-term therapy is at present usually confined to the winter months and to patients with symptoms of pulmonary insufficiency or recurrent invalidism from bronchitis, as the treatment has not yet been completely evaluated. A tetracycline (250 mg. orally four times a day) is probably the drug of choice (*4*). A smaller dose of tetracycline (250 mg. twice a day) is no more effective than phenoxymethylpenicillin (312 mg. twice a day, equivalent to 1 million units daily),* and reduces the duration, but not the numbers, of acute exacerbations.

Acute exacerbations of chronic bronchitis should be treated promptly with a tetracycline or penicillin plus streptomycin.

Bronchiectasis. The problem is similar to chronic bronchitis from a chemotherapeutic point of view, and long-term antibiotic therapy combined with postural drainage is useful.

Whooping-cough, Hæmophilus Pertussis. Chemotherapy is needed in children who are weak, have damaged lungs or are under three years old. A tetracycline is given as it is just as effective and also safer than chloramphenicol (*2*). Chemotherapy is useless unless begun in the first week of illness, nor is it dramatically effective, which is why it is not advocated in all cases. Vomiting may render chemotherapy difficult and it will be rare that parenteral therapy is justified.

Atropine methonitrate is dubiously claimed to have a special antitussive effect in whooping-cough. The usual antitussives may also be tried.

Bacterial Pneumonias. For acute lobar pneumonia, which is always due to pneumococcus, penicillin is always effective. Sulphonamides may be used instead.

---

* Francis, R. S., and Spicer, C. C. (1960). *Brit. med. J.*, (*i*), 297.

Bronchopneumonia is caused by a variety of organisms. Bacteriological identification is very desirable and, if the fever does not fall in two days, essential as a guide to treatment, but in its absence penicillin plus streptomycin offers a wide range of antibacterial effect. If injections are not practicable a tetracycline may be substituted. For staphylococcal pneumonia, see p. 54.

Prophylaxis of Pneumonia. Antibiotics are sometimes used for this purpose, for instance before surgical operations in bronchitic patients. Treatment should be commenced immediately before or immediately after the operation. If it is given for several days beforehand resistant organisms are liable to appear in the lung and postoperative pneumonia may occur, the very event which the treatment was intended to prevent.

The temptation to use prophylactic antibiotics in measles and other diseases should be resisted, for it is by no means certain that they confer any benefits. There is evidence that in hospitalised patients chemoprophylaxis is effective in preventing complications of measles. However, measles is usually treated at home, so that a study of the complication rate of patients in whom chemoprophylaxis was begun at home, in the absence of any secondary infection, is especially interesting (5). Amongst 130 patients receiving chemoprophylaxis the bacterial infection rate was 30%, whilst amongst 298 untreated it was 15%. Antibiotics do not prevent pneumonia in patients with congestive cardiac failure (7), and probably not in unconscious patients.

Virus and Rickettsial Pneumonias are unaffected by antimicrobials with the exception of psittacosis and Q fever which are sensitive to the tetracyclines. Chemotherapy may be needed to control bacterial complications.

Empyema is treated according to the organism identified and by aspiration and drainage. Both systemic and intrapleural chemotherapy is essential. Most antibiotics may be used intrapleurally but soluble penicillin is most often indicated. 1 million units is injected after each aspiration until the fluid is sterile. If the pleural fluid is thick with fibrin or pus so that aspiration is difficult and loculation seems likely, then proteolytic enzymes from the hæmolytic streptococcus, streptokinase-streptodornase mixtures, may be used locally to liquefy the effusion. Living cells are not attacked, but undesirable reactions, such as fever, leucocytosis and casts in the urine are common. Anaphylaxis occurs. The enzymes interfere with blood coagulation and should not be used if recent hæmorrhage has occurred at the site of application. They may also be used in treating any chronic suppurative lesion where liquefaction of purulent material might be an advantage. They have been used in attempts to counter the development of loculation in meningitis and to liquefy hæmatomata. They have been administered systemically with toxic, but not, so far, therapeutic effects. Preparations of trypsin may be used similarly and toxic effects are also common. The use of these enzymes should not be lightly undertaken.

Pulmonary Abscess is treated similarly to bronchopneumonia and with surgery as required.

Pulmonary Tuberculosis is discussed on p. 65.

Bacterial Endocarditis (*9*)

Acute bacterial endocarditis presents as a more urgent problem than does the commoner subacute variety. The diseases are treated similarly. Every effort should be made to identify the organism, which in the subacute variety is usually Strept. viridans (80% of cases) or Strept. fæcalis (10% of cases).

High doses of bactericidal drugs are required because the organism is relatively inaccessible in the avascular valve vegetations and the lack of inflammatory reaction renders bacteriostatic drugs less satisfactory, some organisms surviving and causing relapse. Treatment may be chosen thus:—

Streptococcus Very Sensitive to Penicillin. At least 2 million units of penicillin a day parenterally in divided doses.

Streptococcus Moderately Sensitive to Penicillin. At least 4 million units of penicillin a day parenterally in divided doses *plus* streptomycin 0·75 G. twice a day. The dose of penicillin should be adjusted in the light of quantitative bacteriological sensitivity tests, the aim being to achieve blood levels at least five times as high as the concentration needed to *kill* the organism *in vitro*. Sometimes as much as 20 million units of penicillin per day may be necessary, particularly with Strept. fæcalis.

Miscellaneous Organisms. Treatment depends on identification and sensitivity tests.

Unidentified Organism. Penicillin (4 million units a day) plus streptomycin should be used. If a good clinical response is not obtained within a week the penicillin dose should be increased to 20 million units a day.

Duration of Treatment should be at least six weeks, or four weeks after clinical cure, whichever is the longer, although an occasional embolus does not necessarily mean the infection is still active.

Probenecid may be used to delay renal tubular excretion of penicillin, but apart from reducing the volume of intramuscular injections it is no better than simply increasing the dose of penicillin. With an exceptionally resistant organism it might be used, and it is useful in children whose muscle bulk may be insufficient for the injections. In general, children with endocarditis should be given adult doses of antimicrobials.

Prophylaxis of bacterial endocarditis. Any surgical manœuvre, especially dental extraction, may cause a bacteræmia. This is liable to result in bacterial endocarditis in patients with acquired valvular heart disease or congenital cardiac abnormality. Chemoprophylaxis with penicillin should always be undertaken in such patients. It should be started just before the operation with only sufficient time allowed for the chosen preparation to produce adequate blood levels (oral 60 minutes, i.m. procaine penicillin one to three hours, soluble penicillin 15 minutes). Therapy should be continued for 36 hours, or longer if tissue trauma is extensive, especially after operations in the mouth which is normally inhabited by Strept. viridans. To begin prophylaxis days before the operation may reduce the incidence of bacteræmia, but this is less important than the possibility of encouraging resistant organisms in the body which may then lead to a penicillin-resistant bacterial endocarditis.

Meningitis

Accurate bacteriological diagnosis may be the main factor in determining the fate of the patient. (For tuberculous meningitis, see p. 67.)

Even in the presence of an epidemic there cannot always be complete certainty when the patient is first seen, so there is something to be said for injecting penicillin into the subarachnoid space when the initial essential lumbar puncture is performed, if the fluid is turbid and the patient very ill.

In the absence of bacteriological diagnosis a combination of penicillin (systemic *and* intrathecal) and sulphonamides (oral or parenteral) is probably best. Sulphonamides should never be injected intrathecally.

Meningococcal Meningitis. Sulphadiazine in high dose is the drug of choice. Penicillin may be used instead (systemic and intrathecal) in mild, and both drugs together in very severe cases.

In an epidemic prophylaxis with sulphadiazine or penicillin may be attempted, with doses as in the prophylaxis of rheumatic fever.

Pneumococcal Meningitis is treated by penicillin plus sulphadiazine.

Hæmophilus Influenzæ Meningitis is best treated by chloramphenicol plus sulphadiazine.

For meningitis due to other organisms the general principles of choice of antimicrobial discussed earlier are followed.

Alimentary Tract Infections

Peritonitis. When the causal organism is unknown a broad spectrum drug such as tetracycline is used as infection is usually mixed.

Enteritis. When the causal organism is unknown a sulphonamide may be tried first.

Bacillary Dysentery. An absorbed sulphonamide is highly effective and is preferable to a non-absorbed form because the infection is not confined to the mucous membrane of the bowel and therapeutic amounts are required in the blood. The addition of oral streptomycin may increase the therapeutic effect (*14*). If a patient is dehydrated he will need intravenous fluid and antimicrobials may be injected in this. A tetracycline may be used instead of a sulphonamide if urine volume is dangerously low. Sulphonamide chemoprophylaxis is effective in epidemics.

Typhoid Fever is discussed on p. 45.

Acute Cholecystitis and Acute Cholangitis may be treated with a wide-spectrum antibiotic, such as a tetracycline.

Colonic Surgery is commonly preceded by a course of antimicrobial drug in an attempt to sterilise the colon and prevent complications such as abscess or peritonitis. A non-absorbed sulphonamide (succinyl- or phthalyl-sulphathiazole) may be given for four or five days before surgery or streptomycin orally for three days. If surgery cannot be delayed neomycin is the drug of choice for rapid effect in a day or two. The only reason it is not the drug of choice in all cases is that at present it is extremely expensive. Dosage is given in the sections on the individual drugs.

Urinary Tract Infections

Identification of the causative organism and its sensitivity to drugs are very important because of the large range of organisms which may be responsible and the prevalence of resistant strains. Most of the causative organisms are Gram-negative, but Strept. fæcalis (Gram-positive) is particularly troublesome.

In cystitis and infections of the renal pelvis and ureters it is the concentration of antimicrobial in the urine rather than in the blood that matters, and as many are concentrated in the urine the dose may be relatively low. However, it is the concentration in the blood that matters in infections of the substance of the kidney and in these higher doses are needed.

Correction of predisposing anatomical abnormalities, such as an enlarged prostate, bladder diverticula or congenital abnormalities of the renal pelvis or ureters, or removal of renal calculi, should always be considered. If correction is not possible chemoprophylaxis may help prevent recurrent infections.

A high fluid intake helps to reduce stagnation in the urinary tract and also reduces the danger of crystalluria when sulphonamides are used, but obviously it also reduces the concentration, and so the effectiveness of the antimicrobial drug. A urinary output of about two litres a day is desirable.

Some antimicrobials act best in either acid or alkaline urine. Streptomycin acts best at an alkaline pH, which is also desirable when sulphonamides are used, to reduce the risk of crystal formation. Sodium or potassium citrate is given, usually as the B.P.C. Mixtures (see B.N.F.), to make the urine alkaline; 15 to 30 ml. (containing 3 to 6 G. potassium citrate) at least four times a day are likely to be needed and it is important to test the urine reaction to see that enough is being given. The potassium salt is dangerous, and may even be lethal, to patients with renal failure. Tetracycline is more effective in an acid urine and ammonium chloride, 4 to 6 G. a day in divided doses after meals, has sometimes been used with it, but is not essential and can be dangerous. An acid urine is essential on the rare occasions when hexamine or mandelic acid (p. 63) is used.

It should be remembered that many drugs, such as streptomycin, sulphonamides and the ganglion-blocking drugs, are liable to cause toxic effects at low doses in the presence of renal failure, as a result of reduced excretion. Where the function of one infected kidney is very poor, treatment is especially difficult, since most of the antimicrobial is excreted by the better kidney and the concentration in the urine from the worse side may be low.

In all cases of urinary infection it is desirable to have a specimen of urine sent for bacteriological investigation before treatment begins. However, it is not always necessary to await the result of the examination before beginning treatment. In an acute infection due to an unknown organism it is reasonable to begin with a course of a sulphonamide, but if symptoms persist after three days it is probable that the organism is sulphonamide-resistant and it is reasonable to change to, say, a tetracycline, if bacteriological assistance is not forthcoming.

In chronic infections bacteriological help in the choice of antimicrobial is essential if there is to be a reasonable chance of success. It is essential to perform a test of cure (bacteriological examination after cessation of treatment) before ceasing to supervise the patient, because symptomless chronic infection may have serious, or even fatal, late consequences.

Infections with Pseudomonas pyocyanea and with Proteus can be very troublesome. The former is always sensitive to polymyxin; in the case of Proteus, streptomycin may be effective and, if it is not, nitrofurantoin or big doses of penicillin (10 mega units a day) may succeed.

Nitrofurantoin (Furadantin) is a synthetic antimicrobial useful only against urinary infections because the part that is not rapidly excreted in the urine is metabolised in the body to an inactive form. Its antibacterial spectrum is similar to that of chloramphenicol, and it is often used against E. coli, Proteus and Pseudomonas pyocanea, when these are resistant to other drugs. It is taken orally, after food since it is a gastric irritant. The dose is 50 to 100 mg. 4 to 6-hourly until the urine has been sterile for three days. It is not toxic to the kidney. Hypersensitivity effects (rashes, fever) may occur. Other nitrofurans are available* and some are claimed to be useful in systemic infections although none can be said to have established themselves as essential in therapeutics.

Mandelic Acid and Hexamine (methenamine) are still sometimes used in infections with E. coli or Strept. fæcalis which are resistant to other antimicrobials. Unless the urine is acid they are both quite ineffective.

Mandelic acid is usually given as ammonium or calcium mandelate, but additional ammonium chloride may be needed to make the urine sufficiently acid, *i.e.* less than pH 5·3 tested with a universal indicator paper. Fluid intake should be restricted to 1 litre a day or the concentration of mandelic acid in the urine may be insufficient. Gastric side effects are common. The oral dose is 3 G., 6-hourly, orally, for 10 days when, if the infection persists, mandelic acid should be abandoned.

Hexamine is even less useful than mandelic acid; taken orally it releases formaldehyde in an acid urine in amounts sufficient to reduce bacterial growth. It is more effective in the bladder than in the kidney because time is needed for the release. The oral dose is 1 G. (enteric coated to avoid release of formaldehyde in the stomach) 6-hourly, and 1 to 2 G. ammonium chloride or acid sodium phosphate are taken orally three hours after each dose of hexamine; fluid intake should be restricted to 1 litre a day. Excessive urine acidity or too much hexamine may result in acute hæmorrhagic cystitis which should be treated by large doses of sodium bicarbonate to make the urine alkaline.

The combination of mandelic acid and hexamine (hexamine mandelate, Mandelamine) gives an antibacterial spectrum similar to that of the sulphonamides. The oral dose is 0·75 to 1·0 G. four times a day. The urine must be kept acid by adding ammonium chloride if necessary.

Chemoprophylaxis of Urinary Infections is sometimes undertaken in patients liable to recurrent attacks or acute exacerbations of an ineradicable infection, for instance in recurrent pyelonephritis with polycystic kidneys, recurrent renal calculi or before urological operations. A soluble sulphonamide, 0·5 G. twice a day is used.

Drugs Used in Tuberculosis

Streptomycin and dihydrostreptomycin are discussed on pp. 41–43.

---

* *E.g.* Furaltadone (Altafur). *J. Amer. med. Ass.* (1960), **172,** 1932.

Sodium Aminosalicylate (para-aminosalicylic acid, PAS)

In 1940 it was reported that salicylic acid increased the oxygen consumption and carbon dioxide production of tubercle bacilli. It seemed that this acid or some other benzoic acid derivative might play an important part in the metabolism of the tubercle bacillus, analogous to that of para-aminobenzoic acid in the streptococcus (p. 31). In 1946 fifty related compounds were studied in the hope of finding one which would interfere with the metabolism of the tubercle bacillus sufficiently to offer therapeutic possibilities. As a result of this work PAS was introduced into clinical practice.

PAS is well absorbed from the alimentary tract, is distributed throughout the body water, but it penetrates into the cerebrospinal fluid only partially. The serous cavities are readily accessible. Toxic effects are seldom serious, although nausea, vomiting, abdominal pain and diarrhœa due to local irritation are common. These are less with the sodium salt than with the free acid. Crystalluria, agranulocytosis, fever and hypersensitivity reactions occur. The PAS should be stopped if anything more serious than a mild rash occurs. Goitre with hypothyroidism and diabetes have been reported. Impaired renal function enhances the toxicity of PAS as of so many drugs.

PAS is only used in the treatment of tuberculosis, and always with at least one and sometimes two other drugs (isoniazid and streptomycin) as this delays the development of bacterial resistance to each drug. Dosage of PAS is discussed under the treatment of tuberculosis; it is usually given by mouth as sodium or calcium aminosalicylate cachets. Many patients baulk at the large dose required.

Isoniazid (INH, isonicotinic acid hydrazide)

Isoniazid was introduced as a tuberculostatic agent in 1952. Its discovery was the result of attempts to combine the known antituberculous effects of nicotinamide and the thiosemicarbazones.

Isoniazid is more potent against Myco. tuberculosis than either streptomycin or PAS, it probably acts by interfering with bacterial respiration. It is either bacteriostatic or bactericidal according to concentration and temperature. Isoniazid is well absorbed from the alimentary tract and is distributed throughout the body water, penetrating easily into the cerebrospinal fluid. It should always be given in cases where there is special risk of meningitis (miliary tuberculosis and primary infection). It is active against intracellular organisms, which streptomycin is not. It is partly excreted as an almost inactive metabolite and partly as the active drug. Cumulation occurs if renal function is defective, and chemical estimation of blood levels may be needed to avoid toxicity.

Toxic effects are rare but when they occur they are serious (*13*). Dizziness, twitching of muscles, increased reflexes, insomnia and headache occur. Convulsions are promoted in epileptics and mental disorder in mentally unstable people. Peripheral neuritis occurs and may be prevented, but not cured, by pyridoxine to which isoniazid is an antimetabolite. Constipation and difficult micturition occur. Hypersensitivity reactions have been recorded but are very rare: drug fever, rashes, bronchospasm and blood dyscrasias can occur. If isoniazid is discontinued suddenly mental upset may follow.

Bacterial resistance develops moderately rapidly when isoniazid is used alone, 50% of cases in three months, so it is used in combination with the other agents; although it has been used alone in Africa (*15*).

The usual oral dose is 100 mg. twice a day. The same dose may be given i.m. when circumstances demand it.

Iproniazid (Marsilid) is more toxic than isoniazid. It is a powerful inhibitor of mono-amine oxidase, which isoniazid is not, and induces mental symptoms (p. 210).

Chemotherapy of Respiratory Tuberculosis

Use of one drug alone rapidly leads to development of resistant organisms and brief treatment with a combination is followed by a high relapse rate.

Knowledge of the sensitivity of the organism to antituberculous drugs is useful, but bacteriological tests take weeks to perform and so the information is not usually available before treatment must be begun. About 5% of patients have infections with organisms resistant to one of the three main drugs.

Extremely satisfactory results have been obtained with a variety of drug régimes but it will suffice to quote only one of them. Mild cases (negative sputum, no cavitation) can often be allowed to continue their work.

"In Edinburgh a patient with disease severe enough to require admission to hospital initially receives all three standard drugs. All three drugs are given in case he has been infected with tubercle bacilli resistant to one of them. The other two will then not only be active against the disease but will prevent further resistance developing. Infection with bacilli resistant to two of the main drugs is fortunately rare.

"In patients under the age of 40 we give streptomycin, 1 G. daily, together with sodium PAS, 5 G. three or four times a day, and isoniazid, 100 mg. twice daily. Over the age of 40, as daily streptomycin may give rise to vestibular disturbances, we give streptomycin, 1 G. three times a week, with PAS and isoniazid as before. This does carry a theoretical risk. A patient infected with PAS-resistant bacilli would virtually be receiving intermittent streptomycin with daily isoniazid. It might be more rational to give 0·5 G. of streptomycin daily. But so far we have had no reason to regret our present practice.

"Resistance tests on cultures taken before the start of treatment become available in two or three months. In younger patients, if the bacilli prove to have been sensitive to all three drugs, we omit the PAS and give daily streptomycin and isoniazid so long as the patients are in hospital. Intermittent streptomycin with daily isoniazid is a risky combination, so in older patients we continue streptomycin three times weekly, with daily PAS and isoniazid as before.

"When the patient is discharged from hospital, or in mild cases which do not require admission, it is most convenient to use an oral combination of drugs. The standard combination is 5 G. of sodium PAS and 100 mg. of isoniazid, both given twice daily. For out-patients both drugs are given in the same cachet so as to ensure that they do not take one drug without the other. Unfortunately, we have found that if patients fail to take the full number of cachets isoniazid-resistant organisms may emerge in some cases. . . . In such cases the lower dose of PAS is apparently insufficient to prevent isoniazid resistance even when the isoniazid is reduced *pari passu*. It should be added that we do not use the combination of PAS and isoniazid as initial treatment in patients with severe disease and large bacillary populations. Unpublished information from elsewhere suggests that drug resistance and treatment failure may result in a few such patients" (*12*).

Other combinations of drugs may be necessary according to bacterial resistance or hypersensitivity of the patient, and to the practicability of giving regular injections. It is to be expected that changes in the details of drug treatment will continue to be recommended.

In cases where bacterial resistance to the drugs mentioned above is known to exist a choice will have to be made amongst other antituberculous drugs which are comparatively seldom used because of their relative newness, inefficacy or toxicity: viomycin, cycloserine and pyrazinamide.

Non-respiratory Tuberculosis

The principles of treatment, rest, chemotherapy, surgery, are the same as for respiratory tuberculosis. Chemotherapy may be used to prepare a patient for surgery and also to prevent dissemination of infection by surgery.

Many chronic tuberculous lesions may be relatively inaccessible to drugs as a result of avascularity of surrounding tissues and treatment frequently has to be prolonged, and dosage high.

In Renal Tuberculosis with impaired renal function the dangers of increased toxicity due to defective excretion of drugs should be borne in mind and the dose lowered if necessary. Measurement of the level of drug in the blood is often required.

In Meningeal Tuberculosis* it is essential to use isoniazid, which penetrates freely into the cerebrospinal fluid.

Treatment must be energetic. Maximum doses are used and toxic effects, especially with streptomycin, must be risked.

A typical adult case may be treated with three drugs: streptomycin, 1 to 2 G. a day; isoniazid, 500 mg. a day; PAS, 16 to 20 G. a day for the first 6 to 12 weeks. The streptomycin and isoniazid doses may then be halved until the cerebrospinal fluid has been normal for six months. Isoniazid may be given parenterally only if oral administration is impossible. Sometimes PAS is omitted altogether.

Isoniazid has rendered intrathecal injection of streptomycin unnecessary, although some would still give it in the most severe cases despite the enhancement of neurotoxicity and the chance of spinal block preventing its distribution throughout the subarachnoid space. If used, 20 to 50 mg. of streptomycin sulphate in water is diluted with cerebrospinal fluid and injected very slowly, daily at first and later on alternate days. Streptomycin has been administered by cisternal and ventricular puncture, it is irritant and the cerebrospinal fluid will never become quite normal whilst it is being injected intrathecally.

Tuberculosis of the Skin, particularly lupus vulgaris, usually responds well to isoniazid alone (100 mg. twice a day), resistant cases may require streptomycin as well. Calciferol is obsolete for this purpose.

Duration of Antituberculous Treatment

All patients with tuberculosis should be treated with drugs for at least one year and in most cases for two years. Severe cases may need even longer. In 295 patients with pulmonary tuberculosis, those treated for three months had a relapse rate of 36%, for three to five months, 17% and of those (over 100) treated for a year or more only one relapsed (*12*).

Hypersensitivity to Antituberculous Drugs

Hypersensitivity reactions occur quite often in patients, and sometimes in nurses giving streptomycin injections. The latter can virtually be eliminated by proper technique for preparing the injection; by not producing a fine mist whilst expelling the air from the syringe, and by wearing gloves.

Reactions to isoniazid are rare and the drug should be stopped when one occurs, but if a patient develops a hypersensitivity reaction to either streptomycin or PAS, desensitisation can often be achieved under antihistaminic cover. A suitable régime after a mild reaction would be to start with 100 mg. streptomycin i.m. twice a day, and increase this by

---

* LORBER, J. (1960). *Brit. med. J.*, (*i*), 1309.

100 mg. daily until the therapeutic dose is reached. With a mild reaction to PAS, 1 G. could be given orally on the first day, increasing the dose by 1 G. a day until the required level is reached.

If desensitisation is necessary after a severe reaction, the initial doses should be much lower, starting with 1 mg. streptomycin or 10 mg. PAS and doubling the dose 12-hourly until 100 mg. of streptomycin or 1 G. PAS is reached. The procedure is then as for the mild reactions. If a reaction occurs, a return should be made to a lower dose.

If necessary, even severe hypersensitivity reactions can be suppressed by adrenocortical steroids and desensitisation achieved under their cover. Slow withdrawal of the steroid will soon indicate whether desensitisation has in fact occurred. If it has not it may be necessary to persist with the steroid indefinitely. The value of antihistaminics when steroids are being used is very dubious indeed.

Desensitisation to the antituberculous drugs is generally easier and less dangerous than to penicillin. If a patient is taking all three principal antituberculous drugs and develops a hypersensitivity reaction it is, in practice, usually safe to assume that it is due to streptomycin or PAS and not to isoniazid. If the reaction is mild the drugs are all withdrawn and the patient tested with an injection of 0·5 G. streptomycin. If there is no reaction then streptomycin and isoniazid may be started again and the patient desensitised to PAS. If the initial hypersensitivity reaction is severe it is best to desensitise the patient first to PAS and then to streptomycin. The isoniazid can be begun again at full dosage when the PAS dose reaches 5 G. twice a day.

Adrenocortical Steroids and Tuberculosis

There have been many reports of extension of tuberculous infection following the administration of steroids to patients who have the disease. It is essential that chemotherapy should accompany any such administration. On the other hand, there is some evidence that the steroids may be useful in reducing intense inflammatory reactions, which may be partly allergic, in active tuberculosis and so perhaps enabling drugs to gain readier access to the bacteria. The decision when to use adrenocortical steroids in tuberculosis is one for specialists, as there are at present no generally accepted criteria by which a decision may be reached.

Steroids are also indicated in gravely ill patients who might be expected to die before chemotherapy has had time to produce any benefit (p. 98).

Eye Infections*

Conjunctivitis and blepharitis are caused by a variety of organisms. Solutions and eye-ointments of many antimicrobials, penicillin, sulphacetamide, chloramphenicol and the tetracyclines are available and are often used in conjunction with hydrocortisone. This combination is not to be recommended as the hydrocortisone masks the progress of the infection and, should it be applied with an antimicrobial to which the organism is resistant, may make the disease worse. Local chemoprophylaxis is used to prevent secondary bacterial infection in virus conjunctivitis. Hydrocortisone may make virus infections worse, and delay the healing of some corneal ulcers.

---

* Sorsby, A. (1960). *Brit. med. J.*, (*i*), 1353.

Intra-ocular infections are treated systemically.

Trachoma is due to a large virus; a tetracycline is applied to the eye though it is not certain that the specific virus is sensitive to the drug.

Venereal Diseases

Gonorrhœa

N. gonorrhœæ is usually sensitive to penicillin, but resistant strains do occur. A single i.m. injection of 200,000 units of procaine penicillin cures nearly all uncomplicated cases in the male, but some use twice that dose to be on the safe side. In the female the larger dose of penicillin is needed to ensure cure of infection of the cervix uteri. Oral penicillin may be used, and the tetracyclines are also effective. Chemoprophylaxis with penicillin has been successfully practised in military camps. There is a risk of suppressing the early signs of a simultaneously contracted syphilitic infection so the patient should, if possible, be watched for six months and serological tests for syphilis performed. Some venereologists advocate routine treatment of gonorrhœa with streptomycin (a single i.m. injection of 1 G. for men and 1 G. daily for five days for women) because it has no effect on spirochætes and the danger of masking a simultaneous syphilitic infection is avoided.

Complicated cases of gonorrhœa require therapy for a longer time.

Syphilis

Treponema pallidum never becomes resistant to penicillin.

Primary and Secondary Syphilis is effectively treated by 600,000 units of procaine penicillin i.m. daily, for 10 days. If it is suspected that the patient may not present himself for this course, a single i.m. injection of 5 million units of benzathine penicillin may be given.

Tertiary Syphilis should have the same treatment prolonged to three weeks. The cerebrospinal fluid does not return to normal for months, and sometimes never. A second course of penicillin is advisable if the spinal fluid is still abnormal after six months.

Congenital Syphilis in the newborn may be treated with 200,000 units of procaine penicillin i.m. for 10 days. Topical application of hydrocortisone to the eyes helps to reduce interstitial keratitis.

A Pregnant Woman with Syphilis should be treated as above, in each pregnancy some advocate, in order to avoid all danger to the children.

Therapy is best given between the third and sixth months as there may be a risk of abortion if it is given earlier.

Results of Treatment of Syphilis with penicillin are excellent, virtually 100% cure is achieved in seronegative cases, but the cure rate is lower in seropositive cases. For this reason it is sometimes advocated that a course of Bismuth Injection, B.P. (2 ml. i.m. weekly for 10 weeks) should be given in all seropositive cases.

Follow-up of all cases is essential, for five years if possible, with annual serological tests and a final examination of the cerebrospinal fluid. Relapses are rare and it is not easy to distinguish these from re-infections. One study found the "relapse rate" amongst patients on identical treatment to be related to social status, which suggests that most relapses are really re-infections.

Chemoprophylaxis of syphilis may be practised with oral penicillin, but is not absolutely reliable and there is a risk of contracting an infection, the early signs of which may be masked. Masking of gonorrhœa does not occur. Chemoprophylaxis is not to be recommended under normal social conditions. A patient who is known to have been exposed to syphilis recently may be given 1 to 2 million units of benzathine penicillin, i.m., but there is no agreement as to the clinical merits of this, although social requirements may occasionally demand it. It is probably best to treat the patient as though he has syphilis rather than to risk masking the disease.

Patients hypersensitive to penicillin may be treated with a tetracycline 2 to 3 G. a day for two to three weeks, but with this dose toxic effects are likely. Smaller doses may be effective but it is not known for certain.

There is wide variance in dosage practised in different clinics. As long-term follow-up results become available, dosage will be standardised. Arsenic certainly, and bismuth perhaps, have been rendered obsolete by penicillin. Iodides, under whose sole influence gummata will heal without any concomitant cure of the disease, add nothing to the efficacy of penicillin in late syphilis.

Pyrexial Therapy by deliberate infection with malaria or by heating the patient in a box, is now only used in the most advanced cases with optic atrophy or apparently treatment-resistant neurosyphilis. The treatment has dangers and may confer no benefit when given after a full course of penicillin, but in the absence of definite evidence it is reasonable to retain such desperate measures for such desperate cases (see bismuth sodium thioglycollate).

The Herxheimer (or Jarisch-Herxheimer) Reaction may be due to the massive slaughter of spirochætes resulting in the release of toxic substances. As a simple pyrexia it is common during the few hours after the first penicillin injection. It is usually mild, but in neuro- or cardiovascular syphilis there may be a sudden worsening of the condition due to inflammatory reaction at the site of the lesions. It cannot be prevented by graduating the doses of penicillin, and probably not by using bismuth or mercury first, although in aortic disease there is nothing to be lost by trying a course of bismuth (as above) before starting the penicillin.

Non-gonococcal Urethritis is a heterogeneous group and often responds to a tetracycline.

Chancroid is due to Hæmophilus ducreyi, it is susceptible to penicillin, sulphonamides and to the tetracyclines.

Lymphogranuloma Venereum, due to a large virus, is best treated by the tetracyclines. Early treatment is obviously desirable in the hope of avoiding the dangerous scar formation characteristic of the disease.

Granuloma Inguinale, due to a virus, may respond to a course of a tetracycline.

The use of the tetracyclines in the last four diseases may mask syphilis, so long-term follow-up is desirable.

Vaginal Infections

Bacterial vaginal infections are treated according to general principles of chemotherapy. Resistant infections sometimes respond if a small dose of an œstrogen is given orally for a month. Trichomonas vaginitis may be treated in a variety of ways; the arsenical, acetarsol, is effective as a pessary inserted high in the vagina each night and reinforced by insufflation of acetarsol powder twice a week (but the latter *not* during menstruation or pregnancy). Treatment of the acute phase should last a month and the vaginal tablets should be inserted during menstruation for a further two months. Local hypersensitivity to drugs is common and may be difficult to distinguish from exacerbation of the infection. There are numerous causes of failure to cure and numerous practical details of therapy that are beyond the scope of this book, but which are vital for success.[*]

Monilia vaginitis may be treated by local painting with a 1% solution of gentian violet three times a week. Alternatives are local use of di-iodohydroxyquin (Diodoquin), phenylmercuric nitrate or mercurochrome. Nystatin vaginal tablets are available.

Other Infections

Abscesses and Infections in Bone and Serous Cavities are treated appropriately to the organism concerned but require high doses because of poor penetration. Local instillation of the drug may be needed. These infections are often staphylococcal and if so, treatment follows the lines discussed on p. 54.

---

[*] JEFFCOATE, T. N. A. (1957). Principles of Gynæcology. London: Butterworth.

Chickenpox and Smallpox may require chemotherapy for the inevitable skin sepsis if it is very severe. Penicillin or a tetracycline will serve.

Acute Brucellosis responds to a tetracycline but the relapse rate is high unless streptomycin is given concurrently. High doses are needed for at least two weeks. Mild Herxheimer reactions may occur at the start of treatment.

Chronic Brucellosis is treated similarly but relapse is common and further courses may be needed.

Actinomycosis. This fungus infection is usually treated with penicillin, at least 5 to 10 million units a day for several weeks. In resistant cases there have been favourable reports of isoniazid, the tetracyclines and hydroxystilbamidine.

TROPICAL DISEASES

Amœbiasis

In amœbiasis drugs are required to act locally in the bowel (both on the amœbæ and secondary invading organisms) and systemically in bowel wall, liver and elsewhere (on the amœbæ). This cannot be achieved by one drug alone and so mixed therapy is needed. There is no general agreement on the best combination. The following account gives details which are only of importance to doctors who see cases of amœbiasis.

Ipecacuanha and Emetine

Ipecacuanha is the dried root of a South American plant. Apart from its occasional use in Dover's powder (ipecacuanha plus opium, p. 157) it is obsolete. The alkaloid emetine which it contains is used as an amœbicide, especially in amœbic hepatitis. It is inactive against amœbic cysts and so is useless in carriers. It is obsolete as an emetic, because of toxicity and variable response, but retains its unsuitable name. Emetine is too irritant to be used by mouth. As an amœbicide it is administered by deep s.c. or i.m. injection; both are painful; intravenous injection is dangerous and should not be used. It is slowly excreted by the kidney and daily injections may be cumulative.

Toxicity of Emetine

Local inflammatory reactions to the injection are common. Nausea, vomiting (by a central action) and diarrhœa (by an action on intestinal muscle) occur, and these may be confused with the symptoms of amœbiasis. Emetine is toxic to the myocardium, causing arrhythmias, and to the kidneys. It is unsafe in patients with cardiovascular disease, and all patients should be in bed, if possible, during a course of parenteral emetine.

Treatment of Amœbic Dysentery (see table)

ACUTE AMŒBIC DYSENTERY. Emetine is followed by emetine bismuth iodide plus di-iodohydroxyquin (Diodoquin) or by chlortetracycline instead.

IN CHRONIC AMŒBIC DYSENTERY emetine bismuth iodide plus di-iodohydroxyquin or chlortetracycline is given.

IN CARRIERS, di-iodohydroxyquin or chlortetracycline may be used.

For relapses or cases which fail to respond to emetine, varying combinations may be chosen from the drugs in the table and many others.

SOME DRUGS USED IN THE TREATMENT OF AMŒBIASIS

Drug	*Type of Amœbiasis for which it is used*	*Route of Administration and whether absorbed. Toxicity*	*Dose and Duration of Therapy*
emetine hydrochloride	hepatitis, abscess, acute intestinal	subcutaneous. toxicity: see text	60 mg. a day for 10 days
emetine bismuth iodide	intestinal, acute and chronic	oral, emetine released in bowel and partially absorbed. toxicity: as emetine	200 mg. a day for 7–10 days
chloroquine	hepatitis and* abscesses	oral, absorbed. toxicity: gastro-intestinal upset, itching	900 mg. a day in 3 doses for 7–10 days
di-iodohydroxyquin (Diodoquin)	chronic intestinal	oral, largely unabsorbed. toxicity: as iodide	1 to 2 G. a day in 3 doses for 3 weeks
carbasone (an arsenical)	chronic intestinal (of doubtful efficacy)	oral or rectal, absorbed. toxicity: as arsenic, dangerous in hepatitis	0·5 G. a day in 2 doses for 10 days
chlortetracycline, erythromycin	intestinal, acute or chronic	oral, absorbed. toxicity: see under individual drugs	Dose, see under individual drugs, for 10 days

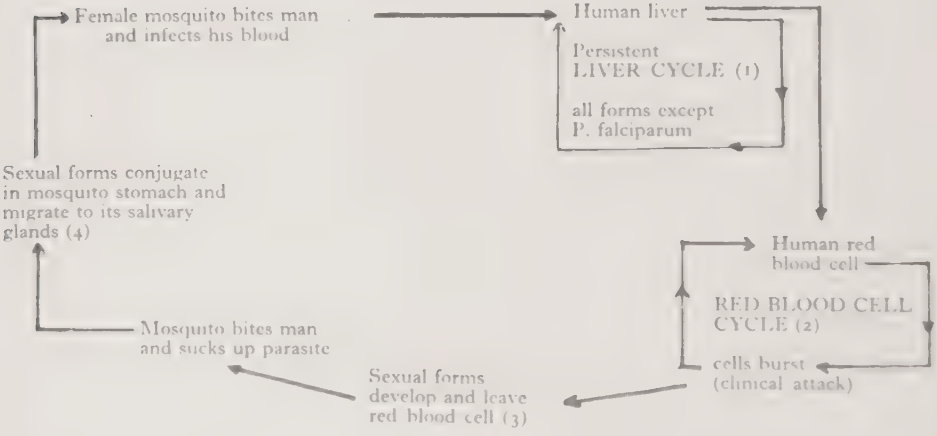
* Chloroquine is concentrated in the liver.

Cholera

The clinical course of cholera is little influenced by chemotherapy. A tetracycline or chloramphenicol is active against the vibrio and so are sulphonamides. It is perhaps best to give an unabsorbed sulphonamide because of the likelihood of renal blockage resulting from the intense dehydration and low urinary volume characteristic of the disease.

Malaria

To understand the chemotherapy of malaria it is necessary to know the principal features of the parasites' life cycle, because complete cure will not result unless both the blood and tissue cycles in the human body are attacked. As this cannot at present be done by a single drug, two drugs must be used, except in falciparum malaria in which the liver cycle does not occur. The correct choice is important.


Female mosquito bites man and infects his blood
Human liver
Persistent LIVER CYCLE (1)
all forms except P. falciparum
Sexual forms conjugate in mosquito stomach and migrate to its salivary glands (4)
Human red blood cell
RED BLOOD CELL CYCLE (2)
Mosquito bites man and sucks up parasite
cells burst (clinical attack)
Sexual forms develop and leave red blood cell (3)

Quinine as cinchona bark was introduced into Europe from South America in 1633. It was used for all fevers, amongst them malaria. Further advance in the chemotherapy of this disease was delayed until 1880, when Laveran finally identified malarial parasites in the blood. His views were not generally accepted and six years later, Osler, at a meeting in the U.S.A., expressed grave doubts of the relevance of Laveran's "bodies". The subsequent discussion so impressed him that he put off his holiday in Canada to investigate the blood of malarial patients. He found the parasites and said that he "had been taught the folly of scepticism based on theoretical considerations".

The mode of spread of malaria was still uncertain when in 1894 Manson while walking along Oxford Street, London, told Ross to "look for the parasite's dung in the mosquito's stomach". Ross returned to India with a microscope, followed this advice and soon provided the final link in the malarial parasite's life cycle.*

Quinine was the principal antimalarial drug available until 1930, when as a result of research based on Ehrlich's work on dyes, mepacrine, also known as Atebrin or Quinacrine, a dye derivative, was introduced. It did not displace quinine until in 1942 the Japanese armies captured South East Asia and the Pacific Islands, which had supplanted South America as the source of quinine. This shutting off of quinine supplies from the Allied forces precipitated a military crisis and mepacrine was hastily manufactured to meet it. The proper use of mepacrine reduced the malaria rate amongst Australian troops in New Guinea from 740 cases per thousand soldiers per annum in November 1943 to 26 cases per thousand soldiers per annum one year later. So important was the prevention of clinical malaria to the prosecution of the war that the daily taking of mepacrine was made a matter of military discipline. Fairley records how some soldiers with malaria were found to have low levels of mepacrine in their blood and how, after having excluded other causes, the "suggestion" that they would be kept "in the North" until their malaria stopped was followed by a dramatic rise of mepacrine blood level and cessation of malaria.

It was vital that the dosage of mepacrine necessary to enable troops to fight in hyperendemic areas without serious casualties from malaria should be found quickly. At a base in North Queensland, Australia, extensive experiments were carried out. Physical stress is believed to promote malarial relapses and so the trials of mepacrine were carried out on volunteers under conditions simulating those of jungle warfare. Volunteers were first exposed to the bites of infected mosquitoes. They were then injected with adrenaline or insulin, put half-naked into, and kept immobile in, a refrigerator at −9°C. for one hour or "worked or exercised in a tropical climate at the hottest time of the year to a point verging on physical exhaustion". Some were "taken over hills for 6–10 miles, induced to swim against a stream until they were tired out, and were then walked back over the hills at as fast a pace as possible by a specially trained sergeant-major". Others marched 80-85 miles over mountains in three days or were put into a decompression chamber. Mepacrine was an effective prophylactic under all these conditions.†

Since this time numerous antimalarial drugs have been discovered and there is a wide choice of remedies.

---

* Russell, P. F. (1953). *Lancet*, (*ii*), 944.

† Fairley, N. H. (1945). *Trans. Roy. Soc. Trop. Med. Hyg.* 38, 311.

Prevention of Malaria

In places where malaria is endemic it is necessary to take drugs regularly to prevent the disease. The ideal drug has yet to be found. Drugs used to prevent malaria are divided into two groups:—

Causal Prophylactics are drugs which act on the parasite *before* it enters the red blood cell cycle, preventing its establishment in the body and eradicating it from the liver if it is already there. They act at site (1) on the life cycle chart on p. 74. Primaquine and pentaquine are effective but too toxic for continuous use: they are only used for achieving radical cure. Proguanil and pyrimethamine are effective causal prophylactics only against Plasmodium falciparum. There is thus no completely satisfactory causal prophylactic available.

Suppressives are drugs which act on the red blood cell cycle of the parasite preventing and curing clinical manifestations (site 2 on the life cycle chart), but not preventing establishment of the parasite in the liver (site 1). Chloroquine, proguanil, pyrimethamine or amodiaquine can be used. Quinine is obsolete because very high doses are needed against P. falciparum and because when used against this parasite, acute hæmolysis (blackwater fever) is liable to occur from an auto-immune mechanism.

Suppressive drugs should be continued for at least two weeks after ceasing to be exposed to infection in order to allow all liver forms to develop into red-cell forms and be killed by the drug. In addition it is desirable to prevent transmission, *i.e.* to render the patient non-infective to mosquitoes. This can be done by the somewhat toxic pentaquine or primaquine which destroy the sexual forms (site 3 of the life cycle) and by proguanil or pyrimethamine which prevent their development in the mosquito (site 4).

Treatment of Malaria

Treatment of the Acute Clinical Attack is best accomplished by drugs which act on the red blood cell cycle, but which unfortunately leave the liver forms untouched. Chloroquine and amodiaquine are the drugs of choice and may be given parenterally in severe cases. Relapses are usual if the treatment is not combined with drugs to affect the parasites in the liver, except in P. falciparum infections where liver forms do not persist.

Radical Cure can only be achieved by giving primaquine or pentaquine which act on the liver cycle, as well as the drugs necessary for the acute attack, so that the liver cycle is eradicated and relapse prevented. P. falciparum has no persistent liver cycle and so radical cure is effected by drugs effective against the red blood cell cycle only (*e.g.* chloroquine, amodiaquine).

THE USES AND TOXICITY OF ANTIMALARIAL DRUGS

Drug	PREVENTION		*Trans-mission preven-tion*	*Treat-ment of clinical attack*	*Radical Cure*	*Disadvantages*
	Causal Prophyl-axis (Act on liver cycle)	*Suppres-sion (Act on red blood cell cycle)*				
chloroquine and amodiaquine	—	+	—	+	P. falciparum only	Toxic effects few and mild as used in malaria: alimentary upsets, headache, visual disturbances. High doses over long time as in rheumatoid arthritis may cause serious ocular damage.
mepacrine	—	+	—	+	P. falciparum only	Toxicity greater than chloroquine: yellow skin, mental changes and digestive tract upsets.
proguanil (Paludrine)	+ P. falciparum only	+	+	+ but slow onset, unsatisfactory	P. falciparum only	Plasmodia may become drug resistant. Toxicity very slight: digestive tract upsets, albuminuria, hæmaturia.
pyrimethamine (Daraprim)	+ P. falciparum only	+	+	+ but slow onset, unsatisfactory	P. falciparum only	Plasmodia may become drug resistant. Toxicity very slight: digestive tract upsets. Theoretically it might cause abortion, so avoided in pregnancy until further data available.
quinine	—	+ unreliable	—	+	—	Toxic effects common in high doses: cinchonism, blindness, hypersensitivity, hæmolysis, abortion.
primaquine and pentaquine	+ but too toxic for use	—	+	—	+ all forms	Toxicity moderate: digestive tract upsets, acute hæmolytic anæmia (esp. in coloured people). Toxicity may be potentiated by mepacrine or proguanil. Pamaquine is obsolete.

The Antimalarial Drugs (see table, p. 77)

The detailed dosage of antimalarials is only of importance to those treating the disease and will be found in Appendix B.

Bismuth Sodium Thioglycollate (Thio-Bismol) is the only antimalarial bismuth salt. Its sole use is to regulate malaria induced for therapeutic purposes, which, if induced by injecting infected blood, is liable to cause daily bouts of fever. It will, if given during the fever on one day, prevent fever the following day, and so is useful if the patient is too weak to stand more. Other antimalarials cannot be relied on to stop the next attack. The drug is a suppressive only and does not cure.

No further account will be given of the antimalarials appearing in the table, except for quinine which has a wider interest.

Quinine

Quinine, which is obtained from the cinchona tree, has lost much of its therapeutic importance. It is usually described, rather vaguely, as a "protoplasmic poison" which term does not conceal ignorance of its exact properties. It is certainly inimical to most living tissues. It is therefore not surprising that quinine has numerous actions in the body, many of which are of no therapeutic use. It is well absorbed from the alimentary tract, although it is a strong irritant, and causes vomiting by local gastric action as well as by stimulating the vomiting centre. Intramuscular injections are liable to form abscesses; i.v. injections are dangerous, because of hypotension, unless given slowly.

Uses of Quinine

Dilute solutions are used for their bitter taste in tonics and as aperitifs. The antimalarial action of quinine has already been mentioned, the mechanism is unknown.

Effects of Quinine

On the Central Nervous System quinine acts as a feeble antipyretic and analgesic and is included in numerous proprietary mixtures. It interferes with the second and eighth cranial nerves (see under toxicity).

On the Heart quinine acts similarly to its optical isomer quinidine (which see) but is less potent.

On Skeletal Muscle quinine increases the refractory period; this is made use of in patients with myotonia (300 mg. of a salt three times a day) or nocturnal muscle cramps (300-600 mg. of a salt before going to bed), sometimes with considerable benefit. Procainamide is also effective. Cortisone has been claimed to be useful in myotonia as in so many other obscure conditions. The symptoms of myasthenia gravis may be made worse by quinine and this has been tried as a diagnostic test in doubtful cases, but it is unreliable.

On the Pregnant Uterus quinine has a stimulant effect which increases as pregnancy advances. It is widely known to the general public as an abortifacient, but it is unreliable even in lethal doses.

On the Blood. Quinine may cause hæmolysis (blackwater fever) in some patients with recurrent falciparum malaria and in pregnancy; it rarely causes thrombocytopenia and agranulocytosis. These are probably hypersensitivity effects, due to auto-immune mechanisms, as are rashes and asthma. This is well shown by the following bold experiment (*11*):—

A woman who was in the habit of taking proprietary analgesics containing quinine had episodes of epistaxis and purpura and hæmatemesis. Eventually the quinine was suspected and an oral test dose of 5 mg. was given. 1½ hours later she felt ill with headache and pyrexia. The blood platelet count fell from 400,000 to 17,600/cmm. in 3½ hours. The bleeding time was 12 minutes (normal 2 to 5 minutes). It was decided to infuse 200 ml. of her plasma into a normal volunteer who had just taken quinine and who was known not to be hypersensitive to it. An hour later the volunteer felt ill and soon had two rigors with cyanosis, nausea and vomiting. His platelet count fell from 850,000 to 5,400/cmm., he developed petechiæ and his gums bled. The bleeding time was over 18 minutes. He was given oral cortisone and corticotrophin i.v., and made a complete recovery although the platelet count took a week to return to normal. A later transfusion of the patient's serum into the volunteer in the absence of quinine caused no reaction.

It is suggested that quinine forms a complex with platelets and that this becomes antigenic in some people. In the experiment the antibodies formed in the patient were transferred to the volunteer and destroyed his platelets in the presence of quinine.

Toxic Effects of Quinine

Some toxic effects of quinine are common to quinidine, salicylates and cinchophen and the term cinchonism is used to describe them. They consist of interference with the auditory nerve causing tinnitus, deafness and vertigo, and of visual impairment and even complete blindness, the onset of which may be very sudden. The cause of this is disputed, it is probably due to direct toxicity on the retinal cells and not to vascular spasm. In addition quinine causes rashes, nausea, vomiting and diarrhœa with abdominal pain, also fever, hypotension, convulsions and respiratory depression. Ventricular tachycardia happens very rarely. Treatment of quinine poisoning consists in encouraging renal excretion by increasing urinary output and in treating symptoms as they occur. Vasodilators and vitamins in cases of blindness are probably valueless.

Loss of sight can be permanent, but partial or complete restoration is usual. Hypersensitivity to quinine sometimes, but not always, means the patient is hypersensitive to quinidine.

African Trypanosomiasis

If the central nervous system is involved the pentavalent arsenical tryparsamide must be used, but if the nervous system is free the less toxic aromatic diamidine (pentamidine) or the dye derivative (suramin or Antrypol) may be substituted. These drugs do not affect South American trypanosomiasis.

Tryparsamide

Tryparsamide is given once a week for 12 weeks; 2 to 3 G. are given i.v. in 10 ml. distilled water; i.m. injections may be used if essential. The course may have to be repeated. Trypanosomes may become drug resistant. Tryparsamide is largely excreted unchanged in the urine. Toxic effects include liver damage, alimentary tract symptoms and hypersensitivity reactions. The most notable undesirable effect is visual disturbance which may proceed to total blindness with optic nerve atrophy. The drug should be stopped at the first visual symptom. Measurement of the patient's visual acuity and size of visual fields before and during treatment is desirable where practicable. Arsenical encephalopathy or myelopathy, and renal and bone marrow damage are very rare or do not occur with tryparsamide but are well recognised with other organic arsenicals. Rashes, including fatal exfoliation occur. Treatment of serious arsenic toxicity is by dimercaprol (p. 431). Nitritoid crises (so called because they resemble effects of amyl nitrite overdose), with circulatory collapse may occur immediately after intravenous injection. Tryparsamide is the least toxic of the organic arsenicals.

It is convenient, because of the very limited therapeutic use of arsenic, to deal with the whole topic here.

Organic Arsenicals. In addition to tryparsamide which is ineffective against early syphilis, there are oxophenarsine, neoarsphenamine and sulpharsphenamine, which were widely used in syphilis until displaced by penicillin. Toxicity of these compounds is similar to, but greater than, that of tryparsamide. They are administered i.v., being liable, like all arsenicals, to cause tissue necrosis if given i.m. or s.c. Organic arsenicals may also be used against yaws and relapsing fever, against chronic amœbiasis (carbasone, orally) and in trichomonas vaginitis (acetarsol, vaginal tablets).

Inorganic Arsenic, once widely used in therapeutics, now has no use except occasionally as an empirical remedy in psoriasis. It should not be used in tonics. Acute poisoning causes violent gastro-enteritis. Chronic poisoning causes weakness and lassitude, coryzal symptoms, salivation, stomatitis, gastro-intestinal upset, dermatitis, increased pigmentation, keratosis, jaundice, renal damage and falling hair and nails. Capillary damage leads to localised œdemas, *e.g.* of eyelids. Peripheral neuritis, encephalopathy and bone marrow depression occur.

Treatment of all forms of arsenic poisoning is by dimercaprol (p. 431).

Aromatic Diamidines (pentamidine). Because the trypanocidal action of suramin was thought to be due to interference with the parasites' carbohydrate metabolism it was decided to test substances known to cause hypoglycæmia in animals for trypanocidal activity. It was soon found that trypanocidal and hypoglycæmic effects were independent, but after testing many new chemicals the therapeutic effect of aromatic diamidines was uncovered in 1938.

Pentamidine may be given i.m., which is painful, or i.v. which is dangerous, although the brisk fall in blood pressure and other histamine-like symptoms may be prevented by previous administration of an antihistaminic.

A therapeutic course of pentamidine consists of 10 to 15 injections of 200 mg. of the isethionate in 10% solution i.m. to which 200 mg. procaine may be added to reduce pain.

Suramin (Antrypol) was developed from the work of Ehrlich. In 1907 he demonstrated that the dye trypan red had a limited effectiveness against trypanosomiasis in mice. Soon two other dyes, trypan blue and violet, were found to be practicable remedies against the disease in African cattle, but with the commercial disadvantage that they caused the meat to assume an unappetising hue. Further research led in 1920 to the discovery of suramin, a colourless compound related to these dyes.

A course of eleven 1 G. injections in 10 ml. water are given i.v. at weekly intervals; i.m. injection is painful but practicable.

An alternative is to give five doses of suramin followed by five of tryparsamide.

Some advocate a test dose of 250 mg. suramin because intolerance is not rare and may be dangerous if the full dose is given first time.

Toxic effects include "nitritoid crisis" as with organic arsenic, urticaria, hepatic damage, agranulocytosis, hæmolysis, purpura, dermatitis and various other hypersensitivity effects. Renal irritation with albumen, casts and red blood cells in the urine is particularly common and suramin should not be used in patients with renal disease. Urine examination should be carried out two or three times a week during a course. Fatal adrenal cortical failure has occurred. Suramin should be abandoned if any toxic effects appear.

Chemoprophylaxis of Trypanosomiasis may be effected by 200 mg.

pentamidine isethionate every six months, or suramin 2 G. i.v. every three months.

Leishmaniasis (Kala-azar)

Pentavalent antimony compounds are used first, followed by a course of pentamidine (as for trypanosomiasis) if this fails.

Antimony. Inorganic compounds have no place in therapeutics except Antimony Sodium Tartrate Injection, B.P., in schistosomiasis. Their effects are similar to those of arsenic.

Organic antimony compounds are used in various tropical diseases; they are very toxic and cause headache, vomiting, abdominal pain, convulsions, renal damage, jaundice, rashes and cardiovascular collapse. Anaphylactic shock occurs.

Sodium Antimonylgluconate Injection, B.P., is one of the less toxic forms. 15 to 20 mg. per Kg. is given i.m. or i.v. daily for six days for leishmaniasis. It may be repeated after two weeks. Cumulation occurs in patients with renal impairment. Numerous other antimony compounds are available. Sometimes the dose of these compounds is expressed as weight of antimony and sometimes as weight of the salt. It is important not to confuse the two. The value of dimercaprol in antimony poisoning is undecided.

Leprosy

Effective treatment of leprosy is complex and requires much experience if the best results are to be got.

The Sulphones are the drugs of choice. They were found to be effective against common bacterial infections in animals during the flood of research that followed the discovery of the sulphonamides, but they were more toxic than these and so were not used clinically. In 1941 the tuberculostatic effect of sulphones was noted and, as a result, they were tried against leprosy in rats. A successful clinical trial followed in 1943.

They are bacteriostatic and resistance may develop. Treatment must be continued for at least two years and sometimes indefinitely. Toxic effects are common at first and the dose is increased gradually.

Toxic effects include allergic phenomena, hæmolysis, methæmoglobinemia, nausea, vomiting, dermatitis, neuritis, hepatitis and mental confusion.

Dapsone (diaminodiphenylsulphone or DDS) is given orally thus: 100 mg. twice a week for the first month, 200 mg. for the second, 300 mg. for the third and 400 mg. for the fourth and succeeding months. The mean daily dose may not exceed 125 mg. It may be given i.m. Other preparations are available, but as they are probably converted into dapsone in the body and are not therapeutically superior there seems to be no advantage in using them. Allergic reactions are common and cause much difficulty. If severe allergy to dapsone develops, one or more of the newer synthetic antileprotics can be tried.

Other Infections

Anthrax may be treated by penicillin, 3 million units a day, or by a tetracycline, 4 G. a day.

Tularæmia and Plague may be treated by streptomycin, the tetracyclines, sulphonamides or chloramphenicol.

Rickettsial Infections, *e.g.* typhus, respond to the tetracyclines and to chloramphenicol. Relapses are common but are amenable to a further course of chemotherapy.

Psittacosis is due to a large virus; it is treated with a tetracycline. Small, or "true", viruses are unaffected by any antimicrobial drug.

Yaws is due to a spirochæte, it is amenable to penicillin and the tetracyclines.

Leptospirosis is due to a spirochæte; there is no agreement as to the best treatment. Chemotherapy certainly plays only a minor part. Penicillin (10 million units a day) or a tetracycline (2 G. a day) may be tried.

Relapsing Fever is due to a spirochæte and responds to penicillin or a tetracycline.

CHEMOTHERAPY OF WORM INFESTATIONS

Successful eradication of intestinal worm infestation depends on careful adherence to schedules which have been found effective in the past. Drugs used are often toxic to the host as well as to the worm and the purge or enema which usually concludes the ritual is intended to expel both the worm and the chemotherapeutic agent. The aim is to achieve maximum concentration of the drug in the bowel with minimum absorption. As more effective and less toxic drugs are discovered treatment is becoming simpler, which is of especial importance when mass therapy is undertaken in endemic areas.

The details of therapy shown in the table on pp. 84 and 85 are only of importance to people actively dealing with the problem.

It is generally desirable to allow up to a week for recovery before repeating doses of the more toxic anthelminthics.

Schistosomiasis

There are two principal remedies for schistosomiasis, the comparatively non-toxic and ineffective lucanthone and the more toxic antimony

Worm	*Drug*	*Dose*	*Ritual on Day Before Drug*	*Post-Drug Ritual*	*Remarks*
tapeworm (Tænia)	mepacrine hydrochloride	600 to 800 mg. by mouth on empty stomach in morning	fluid diet; mag. sulph. purge at night	4 hrs. after drug, purge with mag. sulph. and give enema. Starve until bowels open	Drug best given by duodenal tube to prevent vomiting. Where practicable search stools for head of worm which may not appear for days. If it is not found, only time will show if cure has been achieved. Male fern must not be repeated for at least a week. *Toxicity:* mepacrine, vomiting and rarely disorientation. Male fern, toxic to bowel, and liver, nervous system (convulsions), and kidney if absorbed. Absorption occurs if there is fat in the bowel so castor oil must never be substituted for mag. sulph.
	male fern filix mas	2 G. by mouth twice 2 hours apart on empty stomach in morning			
roundworm (Ascaris)	piperazine	4 G. piperazine as citrate or other salt on empty stomach *OR* 1 G. piperazine twice a day for 5 days. These doses suit adults and children over 25 Kg.	None	None	Toxicity is minimal: malaise, vomiting. Alternatives are hexylresorcinol and diethylcarbamazine.
threadworm (Enterobius)	piperazine*	For 14 consecutive days give syrup of a piperazine salt. Children under 7 Kg.: 250 mg.	None	None	Toxicity is minimal: malaise and vomiting. Precautions against re-infection from self and rest of family essential.

		once a day. 7–15 Kg.: 250 mg. twice a day. 15–25 Kg.: 500 mg. twice a day. Over 25 Kg. and adults: 1 G. twice a day			
hookworm (Ankylostoma)	tetrachloro-ethylene	4 ml. by mouth (for children 0.2 ml. per year of age up to 4 ml. total)	fluid diet (avoiding fat and alcohol which promote absorption of drug); mag. sulph. purge at night	mag. sulph. purge 2 hrs. after drug. Starve until bowels open	Should not be repeated for 10 days. Toxicity slight if used thus: headaches and vertigo. Chenopodium oil is obsolete as a sole remedy as it is toxic, but a low dose may be used advantageously in combination with tetrachloroethylene: chenopodium oil 1 ml., tetrachloroethylene 4 ml.
	bephenium (Alcopar)	5 G. before breakfast (for children: 2·5 G.)	None	None	Toxicity virtually absent. Effective also against concurrent ascariasis.
trichinella					Treatment is only practicable if diagnosed, and this will be rare, in the initial gastro-intestinal stage. Treat then as for hookworm.
whipworm (Trichuriasis)	dithiazanine (Telmid)†	200 mg. three times a day for 5 days. Repeated if stools still contain ova.	None	None	Toxicity is minimal: malaise, gastro-intestinal upsets. Tetrachloroethylene and hexylresorcinol may be used.

---

* Editorial (1960). *Lancet*, (*i*), 1177.

† Paine, D. H. D. *et al.* (1960). *Brit. med. J.*, (*i*), 770.

compounds. The latter are preferred except in light infections and in young people. Antimony is used as for leishmaniasis.

Lucanthone (Nilodin, Miracil D) is active when given orally. It causes nausea and vomiting, yellow skin and urine, headache, malaise, vertigo and tremors. The dose is 1 G. of the hydrochloride twice a day by mouth for four days (12 mg./Kg. twice a day for children).

Filariasis

Diethylcarbamazine 2 mg./Kg. by mouth three times a day for three weeks may be given. Allergic effects, due to destruction of the filariæ, may be severe and antihistaminics should be given for the first few days at least. Results on the whole are good, but repeated courses may be needed.

Guide to Further Reading on the Chemotherapy of Individual Diseases

(*1*) Bueding, E., and Swartzwelder, C. (1957). Anthelminthics. *Pharmacol. Rev.*, **9**, 329.

(*2*) M.R.C. Committee Report (1953). Treatment of whooping cough with antibiotics. *Lancet*, (*i*), 1109.

(*3*) Wannamaker, W., *et al.* (1951). Prophylaxis of acute rheumatic fever. *Amer. J. Med.*, **10**, 673.

(*4*) Editorial (1959). Antibiotic treatment of chronic bronchitis. *Brit. med. J.*, (*ii*), 1315.

(*5*) Weinstein, L. (1955). Failure of chemotherapy to prevent the bacterial complications of measles. *New Engl. J. Med.*, **253**, 679.

(*6*) Weinstein, L. (1955). The chemoprophylaxis of infection. *Ann. intern. Med.*, **43**, 287.

(*7*) Petersdorf, R. G., and Merchant, R. K. (1959). A study of antibiotic prophylaxis in patients with acute heart failure. *New Engl. J. Med.*, **260**, 565.

(*8*) Fry, J. (1958). Antibiotics in acute tonsillitis and acute otitis media. *Brit. med. J.*, (*ii*), 883.

(*9*) Christie, R. V. (1948). Penicillin in subacute bacterial endocarditis. Report to the Medical Research Council on 269 patients treated in fourteen centres appointed by the Penicillin Clinical Trials Committee. *Brit. med. J.*, (*i*), 1.

(*10*) Barber, M., Csillag, A., and Medway, A. J. (1958). Staphylococcal infection resistant to chloramphenicol, erythromycin and novobiocin. Effect of antibiotic combinations on the emergence of resistant strains. *Brit. med. J.*, (*ii*), 1377.

(*11*) Steinkamp, R., Moore, C. V., and Doubek, W. G. (1955). Thrombocytopenic purpura caused by hypersensitivity to quinine. *J. Lab. clin. Med.*, **45**, 18.

(*12*) Crofton, J. (1959). Chemotherapy of pulmonary tuberculosis. *Brit. med. J.*, (*i*), 1610.

(*13*) Editorial (1958). Neurotoxic effects of isoniazid. *Brit. med. J.*, (*i*), 880.

(*14*) Editorial (1959). Treatment of bacillary dysentery. *Brit. med. J.*, (*ii*), 18.

(*15*) Editorial (1960). Only isoniazid. *Lancet*, (*i*), 1013.

Chapter 5

CORTICOTROPHIN, ADRENOCORTICAL HORMONES

History

In 1855 Dr. Thomas Addison published his famous monograph "On the constitutional and local effects of disease of the suprarenal capsules" in which he had received some assistance in his observations from three of his colleagues. All four have given their names to diseases unrelated to the adrenal cortex; Addison to pernicious anæmia, Bright to nephritis, Gull to myxœdema and Hodgkin to lymphadenoma. In the following year a physiologist whose principal fame also lies elsewhere made a contribution to the study of the adrenal glands. Brown-Séquard performed bilateral adrenalectomy in animals and demonstrated that the glands were essential to life. His work was criticised on the grounds that animals would die of such surgery whether the glands were removed or not.

Before the end of the 19th century attempts were being made to treat patients with Addison's disease by adrenal gland extracts. By 1896, Osler, using glycerin extracts of fresh hog adrenals given orally, had treated six cases with improvement in one.

The fact that there were different secretions from the adrenal cortex and medulla was not appreciated in 1901 when adrenaline was first isolated, so that the failure of attempts to maintain life in adrenalectomised animals and to benefit Addison's disease with the newly discovered hormone resulted in great disappointment.

It was not until the 1920's that the vital importance of the adrenal cortex was appreciated and the distinction between the hormones secreted by the two parts of the gland became clear. At this time it was said "the literature so-called of the physiology and pathology of the adrenal bodies presents a very confused and baffling picture, which only begins to clear somewhat when it is recognised that no mean proportion of the total mass of printed matter, and the portion which contributes most to the haze, can and ought to be stricken from the record on internal evidence alone. . . . Nowhere, perhaps, in experimental work is it more necessary to remember the difference between *post hoc* and *propter hoc*. Anyone who looks into the literature will see how often this rule has been neglected."*

---

* STEWART, G. N. (1924). *Physiol. Rev.*, **4**, 163.

By 1929, a year of grave economic upheaval, a reliable adrenal cortical extract was being prepared and its potency determined on cats. This involved injecting, over a period, some five hundred U.S. dollars' worth of material into each cat. These valuable beasts "were viewed with some economic misgiving by those of us who, as graduate students in the Princeton laboratories at the time, were not sharing in the alleged prosperity of early 1929."* However, the first clinical trial of this extract reassured any doubters by rapidly reviving a moribund patient suffering from Addison's disease.

By 1936, numerous steroids were being crystallised from cortical extracts, but not enough could be obtained to provide supplies for clinical trial.

The first steroid to be synthesised was deoxycortone (DOCA, DCA) in 1937, and this was, in fact, done before it had been isolated from cortical extracts, where it occurs in only very small amounts.

In 1948 cortisone was made from bile acids in quantity sufficient for clinical trial, and the dramatic demonstration of its power to cause remission in cases of rheumatoid arthritis was published in the following year. Since then an embarrassingly large number of steroids have been made and offered to the clinician. They are made by a complicated process from natural substances (ox bile and various plant chemicals), the constitution of which approach most nearly to that of the steroids themselves. A principal aim in research is to produce steroids with more selective action than cortisone, which commonly induces a greater variety of effects than are desired in any patient who is not suffering from adrenal insufficiency.

About the same time as cortisone was introduced, corticotrophin became available for clinical use.

In 1927 it had been shown that removal of the pituitary gland in animals was followed by atrophy of the adrenal cortex. In 1933 it was found that administration of pituitary gland extracts to animals was followed by hypertrophy of the adrenal cortex. In the 1940's the pure substance in the pituitary, corticotrophin, was isolated.

CORTICOTROPHIN

(Adrenocorticotrophic Hormone, ACTH)

Corticotrophin is a polypeptide, consisting of a chain of 39 amino-acids, secreted by the anterior pituitary gland. It is responsible for stimulating the synthesis and/or release of corticosteroids (of which the most important is hydrocortisone) and to a lesser extent of androgens, by the cells of the adrenal cortex. It has only a minor effect on aldosterone production which can proceed independently. In the absence of corticotrophin the cells of the adrenal cortex atrophy. The release of corticotrophin by the pituitary gland is controlled by the hypothalamus by a mechanism which is probably neuro-humoural and which is influenced by environmental stresses as well as by other factors, one of which is the level of circulating hydrocortisone and other glucocorticoids. High blood levels of hydrocortisone prevent release of corticotrophin which in turn results in adrenal hypofunction. This is the reason why steroid therapy must not be stopped suddenly. It must be tailed off to give time for the normal production of corticotrophin to be resumed and, in the case of prolonged therapy, for the recovery of the atrophied gland.

---

* Gaunt, R., and Eversole, W. J. (1949). *Ann. N.Y. Acad. Sci.*, **50**, 511.

The effects of corticotrophin are almost wholly those of the steroids liberated by its action on the adrenal cortex. Prolonged administration leads to adrenocortical over-activity which results in the same ill-effects as excessive corticosteroid therapy (see under cortisone).

Uses of Corticotrophin

Corticotrophin is used both for diagnostic tests and in treatment:—

Diagnostic Use, as a test of the function of the adrenal cortex in cases suspected of Addison's disease, hypopituitarism, Cushing's syndrome or the adrenogenital syndrome. Hypersensitivity reactions may occur during such tests as a result of the injection of this foreign peptide, or a contaminating protein. In cases of Addison's disease, such a reaction may provoke Addisonian crisis (acute adrenocortical insufficiency). The patient can be protected from this risk by the simultaneous oral administration of 1 mg. fludrocortisone, which does not interfere with the test as the amount of steroid excreted in the urine due to degradation of this dose is negligible.

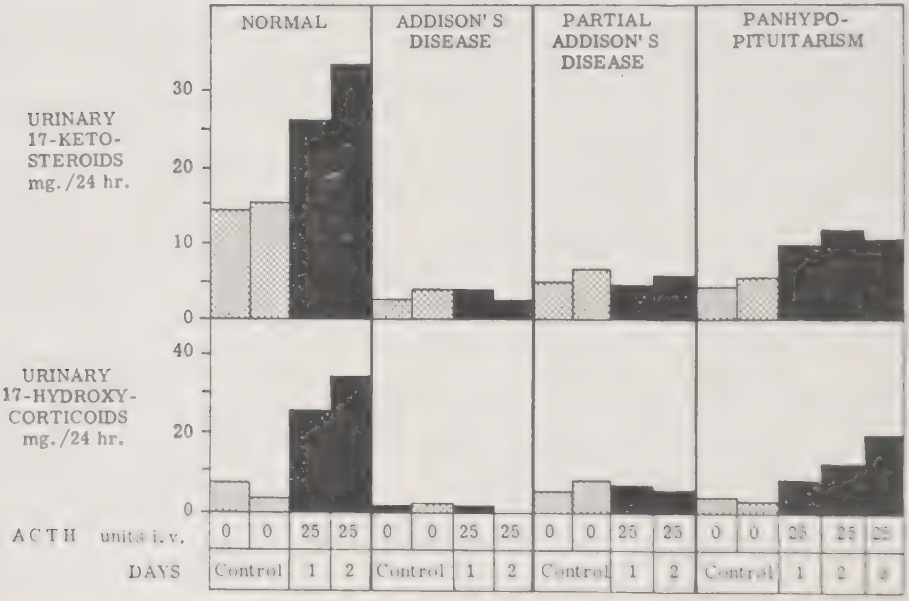
There are numerous methods of performing a corticotrophin test to determine whether, and to what extent, the adrenal cortex can respond to the hormone. One satisfactory technique is to infuse 25 I.U. of corticotrophin i.v., over eight hours on two successive days, with 24-hour urine collection commencing at the time of the infusion.

The response is assessed by the amount of 17-hydroxycorticoid or 17-ketogenic steroid excreted in the urine in excess of that excreted in the control period of 24 hours before the administration of the corticotrophin.

Characteristic responses are shown in the figure on the next page.

Therapeutic Use, either, *a*, when adrenocortical hormone effects are desired to treat a disease or, *b*, when it is desired to stimulate inactive adrenal glands.

a. The aim is to produce intense active adrenocortical stimulation so as to achieve high blood levels of hydrocortisone. Corticotrophin has the disadvantage that it must be given by injection and the effectiveness of the adrenal response is uncertain unless blood or urine 17-hydroxycorticoid levels are measured. In theory corticotrophin is preferable to cortisone and other steroids in diseases associated with muscle wasting, such as dermatomyositis. This is because corticotrophin causes an increased adrenal secretion of anabolic steroids (androgens, excreted in the urine as 17-ketosteroids) as well as of catabolic steroids (*e.g.* hydrocortisone, excreted in the urine as 17-hydroxycorticoids) whereas cortisone is a catabolic steroid and promotes muscle wasting. Cortisone administration is followed by an increase in urinary 17-hydroxycorticoids and a decrease in 17-ketosteroids. The latter is due to pituitary inhibition resulting in adrenal suppression so that even the normal amount of anabolic steroid is not produced. It is not known how important this difference between corticotrophin and cortisone is in clinical practice.



Response to corticotrophin in adrenal insufficiency.
(By courtesy of Dr. George Thorn and the Editor of J.A.M.A.)

b. To stimulate an adrenal cortex which has been inactivated as a result of suppression of the anterior pituitary gland by prolonged steroid therapy (see p. 97).

Preparations of Corticotrophin

These are made from animal pituitary glands and so are liable to cause hypersensitivity reactions, although these are becoming rarer as the preparations become purer. There is great individual variation in response to corticotrophin, which is standardised biologically. There are two kinds of preparation:—

Short-acting Preparations consist of a dry powder which is dissolved in saline immediately before injection. For intense stimulation 20 to 40 I.U. is given i.m., 6-hourly, or the same dose as an i.v. infusion over 24 hours. Continuous infusion is required because the half-life of corticotrophin in the blood is only about five minutes. The plasma level of 17-hydroxycorticoids rises within about two minutes of an i.v. injection of corticotrophin.

Long-acting Preparations have been made to avoid the inconvenience of frequent injections. They are of two kinds. Corticotrophin gel in which the hormone is incorporated in gelatin, and corticotrophin-zinc in which it is adsorbed on a zinc salt in fine aqueous suspension.* For continuous effect 40 I.U. of corticotrophin gel are given i.m. twice a day, or 20 I.U. of corticotrophin-zinc i.m. every second day, as a start, and dosage is then adjusted according to results.

It is important to use the minimum dose for the required response in order to avoid toxic effects (see under cortisone). Contra-indications for corticotrophin are the same as those for adrenocortical steroids.

ADRENOCORTICAL HORMONES AND THEIR ANALOGUES

Hormones normally produced by the adrenal cortex include hydrocortisone (cortisol), aldosterone, corticosterone and some androgens and œstrogens, but not cortisone, which, when administered, is converted in the body into hydrocortisone. Numerous other steroids have been isolated from the gland and many more have been made in the laboratory. In the account that follows, the effects of cortisone will be described and then other steroids chiefly in the ways that they differ.

The effects of cortisone are:—

On Electrolytes: Cortisone administration leads to increased retention of sodium by the renal tubules and to loss of potassium in the urine. It is much less effective than deoxycortone or fludrocortisone in this respect.

On Carbohydrate Metabolism: Cortisone antagonises insulin, gluconeogenesis is increased and peripheral glucose utilisation is decreased so that there is hyperglycæmia and sometimes glycosuria.

On Protein Metabolism: Anabolism is decreased but catabolism continues unabated so that negative nitrogen balance follows. Osteoporosis may occur as the result of this.

Inflammatory Response is depressed, regardless of its cause.

---

* There is also a protamine-zinc suspension.

Allergic or Hypersensitivity effects are suppressed. The antigen-antibody reaction is unaffected, but the injurious consequences do not occur. Antibody formation may be reduced.

Lymphoid Tissue is reduced.

Renal Excretion of Uric Acid is increased.

Blood Eosinophils are reduced in number.

Fat Distribution is altered and deposition occurs over the trunk and in the face. Fat and fluid replace muscle tissue.

Euphoria or psychotic states may be produced.

Wound Healing is slightly delayed, but this is not generally sufficient to be of any practical importance.

Suppression of Pituitary-adrenocortical System occurs so that sudden withdrawal leaves the patient in a state of adrenocortical insufficiency.

Notes on Individual Adrenocortical Steroids Available Clinically

All are active when swallowed except deoxycortone. They are usually given three times a day. Some details of preparations and equivalent doses are given in the table.

THE RELATIVE POTENCY OF THE MAIN ADRENOCORTICAL STEROIDS USED TO OBTAIN ANTI-INFLAMMATORY EFFECTS

Compound	*Size of Oral Tablet*	*Relative Potency*		*Equivalent Dosage (for Anti-inflammatory Effect)*
		Anti-inflammatory (Glucocorticoid) Effect	*Sodium-retaining (Mineralocorticoid) Effect*	
cortisone acetate	25 mg.	1	1	100 mg.
hydrocortisone	20 mg.	1·25	1	80 mg.
prednisone and prednisolone	5 mg.	4–5	0·8	20–25 mg.
6-methyl prednisolone	4 mg.	5–6	minimal	16–20 mg.
triamcinolone	4 mg.	5–6	minimal	16–20 mg.
dexamethasone	0·5 mg.	25–35	minimal	2–3 mg.

Cortisone can be given orally or i.m. Since it is converted into hydrocortisone in the body it has both sodium-retaining (mineralocorticoid) and anti-inflammatory and metabolic (glucocorticoid) effects and so is well suited as replacement therapy of adrenal insufficiency.

Hydrocortisone is the principal naturally occurring steroid. Its effects are similar to those of cortisone. It is the only adrenocortical steroid that can be given i.v. (as hydrocortisone sodium succinate) for rapid effect in emergency. A suspension of hydrocortisone can also be given i.m. as an insoluble salt (Hydrocortisone Acetate Injection, B.P.), which is absorbed more slowly than cortisone and is only suitable for providing a prolonged effect; it is also injected into joints.

Prednisone and Prednisolone have slightly less sodium-retaining effect than has cortisone, but four to five times its anti-inflammatory activity. Prednisolone acetate may be injected i.m.

Methylprednisolone has slightly greater anti-inflammatory power than prednisolone, and much less sodium-retaining activity. It is only available as tablets for oral use.

Triamcinolone is similar to methylprednisolone, but has the disadvantage that muscle wasting may be very pronounced in some patients. It is taken orally only.

Dexamethasone has great anti-inflammatory and trivial sodium-retaining effect. It is taken orally only.

Fludrocortisone has a very great sodium-retaining effect in relation to its anti-inflammatory action, and only at high doses need the non-electrolyte effects be considered. It is taken orally, or applied locally (as a 0·1% ointment or lotion).

Deoxycortone (DCA, DOCA) has almost exclusively sodium-retaining effects. It is destroyed on passage through the liver and hence is ineffective when taken by mouth. It is absorbed from the buccal mucous membrane and sublingual tablets are available. It can be given i.m. in oil for brief effect (24 hours), or as a suspension of an insoluble salt (trimethylacetate) for prolonged effect (15 to 30 days).

Aldosterone is probably the main natural salt-retaining hormone. It is not available for general use. See also p. 313.

The Choice of Adrenocortical Steroid for Clinical Use

This can be summarised:—

For Replacement Therapy in adrenocortical insufficiency, cortisone or hydrocortisone. In Addison's disease a small dose of one of the hormones with only sodium-retaining effects is usually needed in addition.

For Anti-inflammatory Effect, prednisone, prednisolone, methylprednisolone, triamcinolone or dexamethasone. It is not possible to rank these in any order of merit. One or other may suit an individual patient best, especially as regards incidence of side-effects such as muscle wasting, but no prediction can be made. Prednisone is very widely used and gives satisfactory results.

For Sodium-retaining Effect, fludrocortisone or deoxycortone. Aldosterone is not yet available.

Unwanted Effects of Adrenocortical Steroids

The incidence of unwanted effects depends on the type of steroid used, for instance the predominantly sodium-retaining mineralocorticoids seldom cause osteoporosis and the predominantly anti-inflammatory glucocorticoids are unlikely to cause electrolyte disturbance. The following effects may occur; they largely follow from the list of cortisone effects given above: facial rounding, water and sodium retention and hypertension, decreased glucose tolerance, acne, menstrual disorders and worsening of menopausal symptoms, obesity of the trunk, psychological disturbances, bruising and striæ, blood hypercoagulability with thrombophlebitis, reduced resistance to infection, weakness, muscle wasting and osteoporosis, indigestion and peptic ulcers, hæmatemesis and melæna, hypokalæmia, delayed healing of wounds, headache, convulsions and adrenocortical insufficiency on withdrawal of steroid therapy if this has been prolonged.

The incidence of these effects depends on dosage and duration of administration. At least part of the undesirable gastric effects of adrenocortical hormones may be due to local action in the stomach.

It is usual to give 2 to 6 G. of potassium chloride orally daily to patients on prolonged steroid therapy to prevent hypokalæmia, but this is seldom, if ever, required when the steroids are given because of adrenal insufficiency.

Contra-indications to use of adrenocortical steroids therefore include diabetes, peptic ulcer, hypokalæmia, osteoporosis, epilepsy, psychosis or any mental disorder that is not trivial, thrombotic disease and a history of tuberculosis. Tuberculosis may develop insidiously during adrenocortical steroid therapy.* If adrenocortical steroids are required in a patient suffering from active infection of any kind the infection must be treated with appropriate chemotherapy. In the presence of hypertension or potential or actual heart failure, sodium-retaining mineralocorticoids must be avoided. It seems that moderate doses are safe in pregnancy but high doses should be avoided, especially in the first trimester, owing to a theoretical risk of causing fœtal abnormality during that period.

Dosage of Adrenocortical Hormones

This depends very much on the condition in which they are being used and on individual response. It is impossible to suggest a schedule of dosage that will suit every case.

---

* MACKINNON, J. (1959). *Brit. med. J.*, (*ii*), 1375.

The following commencing doses can be used:—

For a disease such as dermatomyositis which may be fatal: prednisone 60 to 75 mg. a day, or its equivalent of another steroid. The dose is then increased if necessary until the disease is controlled or toxic effects occur; as much as 200 to 300 mg. prednisone a day can be needed.

For a chronic, less dangerous disease, such as rheumatoid arthritis: 10 to 17·5 mg. of prednisone daily, adjusted later according to the response.

In some special cases, including adrenal insufficiency, dosage is mentioned in the account of the treatment of the disease.

Equivalent doses of the various steroids will be found in the table on p. 92.

For long-term use the minimal amount to produce the desired effect must be found if serious toxicity is to be avoided. The patient's weight is a particularly valuable and convenient measure for detecting early fluid retention before clinical œdema occurs. Other precautions include a monthly urine test for glucose and a six-monthly spine X-ray for osteoporosis. In general, serious side-effects will not be encountered if the daily dose is kept below the equivalent of 75 mg. of cortisone.

Indications for the Use of Adrenocortical Steroids (*1*)

1. Use is obligatory in adrenocortical insufficiency; as in Addison's disease, Waterhouse-Friderichsen syndrome, hypopituitarism and following adrenalectomy. Adrenocortical insufficiency can also occur in a variety of very severe life-endangering diseases, infections and shock.
2. A wide variety of inflammatory and allergic diseases and diseases of unknown ætiology (see below).
3. Suppression of adrenocortical secretion of androgen by inhibition of the pituitary production of corticotrophin. This is required in the adrenogenital syndrome.

An account of the use of steroids in some individual diseases follows.

Acute Adrenal Insufficiency (Addisonian crisis)

This is an emergency and 100 mg. hydrocortisone sodium succinate should be given i.v. immediately it is diagnosed. An i.v. infusion of 0·9% sodium chloride solution is set up and a second 100 mg. of hydrocortisone sodium succinate is added to the first litre which may be given over two hours. At the time the infusion is started 100 mg. cortisone acetate are given i.m. After the infusion the patient should receive 50 mg. cortisone acetate i.m. or orally, 8-hourly for 24 hours, then 12-hourly for 24 hours and then a total of 50 to 75 mg. a day orally in two or three doses. Other treatment to restore electrolyte balance will depend on the circumstances. Blood transfusion with or without vasoconstrictor drugs may be needed in addition to help restore the blood pressure. The cause of the crisis should be sought and treated; it is often an infection. When the dose of cortisone falls below 75 mg. a day supplementary sodium-retaining hormone may be needed (see below).

Chronic Primary Adrenocortical Insufficiency (Addison's disease)

Cortisone or hydrocortisone orally are used (25 to 50 mg. total daily with two-thirds of the total dose in the morning). The symptoms and signs of Addison's disease regress. Some patients do well on cortisone alone with or without added salt, but most patients require a small amount of sodium-retaining hormone as well as the cortisone (fludrocortisone, 0·1 to 0·2 mg. once a day, orally, or deoxycortone trimethylacetate, 50 to 100 mg. i.m. every two to four weeks). Deoxycortone has no effect other than sodium-retaining at ordinary dosage, but if the dose of fludrocortisone should exceed 0·5 mg. a day, an unlikely event, then its cortisone-equivalent must be taken into account (for metabolic or glucocorticoid effect, 1 mg. fludrocortisone is equivalent to 20 mg. cortisone). The injectable preparations are obviously valuable for patients who are liable to vomit.

The dosage of the hormones is determined in the individual by following his general clinical progress and particularly by observing his weight, cardiac size, blood pressure, presence of œdema, serum sodium and potassium concentration and hæmatocrit.

Thorn reports from a wide experience that the majority of patients with primary chronic adrenocortical insufficiency on 25 to 50 mg. cortisone or hydrocortisone, plus 0·1 to 0·2 mg. fludrocortisone a day orally, have a life expectancy which is equal to that of a normal subject (*1*). If any complicating disease arises, such as infection, a need for surgery or other stress, the cortisone dosage should immediately be increased by 50 to 100 mg. a day. If there is vomiting, the hormones must be given parenterally without delay. Tuberculosis is not a contra-indication to cortisone where there is adrenal insufficiency, but adequate chemotherapy is essential. Some patients (particularly those with hypopituitarism) when first treated, cannot tolerate full doses of cortisone because they become euphoric and otherwise mentally upset. 12·5 mg. a day may be all they can take, but this can usually soon be increased safely if it is done slowly. Patients with peptic ulcer may be unable to exceed 25 mg. of cortisone a day. If diabetes is present the full dose of cortisone is used and the diabetes controlled with insulin. Diabetics should take some of their daily cortisone requirement late at night.

Chronic Secondary Adrenocortical Insufficiency

This occurs in hypopituitarism. In theory the best treatment is corticotrophin but the disadvantages of frequent i.m. injection are such that cortisone is preferred. Usually less cortisone is needed than in primary insufficiency. Special sodium-retaining hormone is seldom required, for the pituitary has little control over aldosterone production so that this hormone is still secreted by the adrenal cortex. Thyroxine is given too. The general conduct of therapy does not differ significantly from that in primary adrenal insufficiency.

Iatrogenic Adrenocortical Insufficiency

This occurs in patients who have received prolonged steroid therapy, which inhibits pituitary production of corticotrophin and so results in atrophy of the adrenal cortex. To avoid an acute crisis on withdrawal, steroid therapy must be withdrawn gradually to allow the gland time to recover under the influence of resumed pituitary function. Also, when a patient taking a steroid has an infection or surgical operation he should be treated like a case of primary insufficiency and corticotrophin can be given to stimulate the atrophic adrenal cortex.

After the use of large doses to suppress inflammation or allergy, sudden withdrawal may not only lead to an adrenal insufficiency crisis but to relapse of the disease which has only been suppressed, not cured. Such relapse can be extremely severe.

Withdrawal of Steroid Therapy may be accomplished thus:—

If, say, 75 mg. prednisone a day has been used it may be reduced to 65 mg. for four days and then by 10 mg. every four days until 15 mg. is reached when it should be reduced by 5 mg. every four days and a single dose of 5 mg. given the day after the last four-day period. Corticotrophin gel 25 mg. i.m. twice a day, should be given on each day of the last four-day period to encourage restoration of the atrophied gland. Complete recovery of adrenocortical function may not occur for three months or even a year, and any intercurrent illness or operative procedure may require resumption of steroid or corticotrophin therapy to avoid collapse. Withdrawal collapse is liable to be very severe as the following case-report* shows: 62·5 mg. cortisone was given daily orally for a month, to a young man on account of a severe rheumatic condition. "... manipulation of the left knee was performed with the patient under thiopentone anæsthesia. Breakfast and cortisone were withheld on this morning. Because of a heavy surgical schedule, the procedure was deferred until early afternoon. The period of anæsthesia was approximately five minutes, and the actual manipulation required only a minute. Recovery from the anæsthesia was somewhat slow. At 6 p.m. it was noted that the patient was awake and alert, but nauseated. He therefore omitted his evening meal and his evening dose of cortisone. At midnight he talked to the ward nurse and apparently seemed to be all right. At 2 a.m. . . . the attention of the nurse was drawn to the patient because of his stertorous respirations. Examination revealed that he was deeply comatose, very cyanotic and drenched with cold sweat . . . pulse rate was 140 per minute and it was weak and thready. Blood pressure was unobtainable by auscultation; by palpation, systolic pressure was judged to be approximately 90 mm. Hg. . . ." He was moribund and comatose for 24 hours, despite full treatment with adrenocortical hormones, noradrenaline and oxygen. He then made a steady and complete recovery. The authors point out that this very serious reaction should have been avoided by giving a depôt preparation of cortisone i.m. before even a trivial operation, and by not allowing a patient to omit a dose of cortisone just at the time when he was probably feeling the first symptom (nausea) of adrenal deficiency. Anæsthesia in adrenocortical insufficiency is discussed on p. 149.

---

* Harnagel, E. E., and Kramer, W. G. (1955). *J. Amer. med. Ass.*, **158**, 1518.

Adrenocortical Steroids in Temporary Insufficiency due to Severe Illness

Adrenocortical steroids are used in severe illness where it is thought that a temporary adrenal insufficiency has occurred, the patient being so ill that his pituitary-adrenal system does not respond to the need for increased steroid output. This may occur in any very severe infection with collapse, and in shock. Such use of steroids is still experimental and undoubtedly carries dangers, for it is established that although patients may look and feel better, and pyrexia may disappear under steroid therapy, bacterial multiplication may actually increase, the steroids having suppressed the normal inflammatory response to invasion. It is therefore essential that such use of steroids in infections should be accompanied by effective chemotherapy. Normal amounts of adrenocortical hormones are required if the body is to resist infection, but excess prevents the normal reaction against infection, so that it is not surprising that the place of these hormones in infections is disputable.

Adrenogenital Syndrome and Adrenal Virilism

An attempt is made to suppress excess adrenocortical androgen secretion by inhibiting pituitary corticotrophin production by means of prednisone or fludrocortisone. Suppression of androgen production is effective if there is adrenal hyperplasia, but not if an adrenal tumour is present. Hairiness, of which female patients complain bitterly, is often unaffected even though good suppression is achieved. The diagnosis and treatment of these patients is beyond the scope of this book. Surgery is often required.

Adrenocortical Hormones as Anti-inflammatory and Anti-allergic Agents

Adrenocortical steroids have been used in virtually every hitherto untreatable or obscure disease, *e.g.* collagen diseases, nephrotic syndrome, sarcoidosis, with very variable results. Only a brief survey can be given here.

The hormones are used in *all* cases of:—

Severe Exfoliative Dermatitis and Pemphigus.

Status Asthmaticus that has not responded to other drugs (p. 258).

Severe Hypersensitivity Reactions of all kinds.

The hormones are used in *most* cases of:—

The following Collagen Diseases: rheumatic fever (p. 175), disseminated lupus erythematosus, polyarteritis nodosa (*10*), scleroderma, dermatomyositis, giant-cell arteritis. If, in the latter disease, vision has been at all affected, steroid administration is urgent.

The hormones are used in *some* cases of:—

Rheumatoid Arthritis (p. 176).

Ankylosing Spondylitis (p. 178).

Ulcerative Colitis (p. 327).

Sarcoidosis, especially if there is hypercalcæmia. It is hoped that steroids will prevent the pulmonary fibrosis of the disease. A course of antituberculous chemotherapy should begin three months before the steroid is started. Sarcoidosis is often self-limiting and the patient should be observed for up to a year in the hope of spontaneous remission before beginning troublesome steroid therapy.

Blood Diseases, due to circulating antibodies, *e.g.* acquired hæmolytic anæmia; thrombocytopenic purpura; agranulocytosis; also acute and chronic lymphatic leukæmia. (Myeloid leukæmia may be made worse.)

Eye Diseases. Allergic diseases and non-granulomatous inflammation of the uveal tract. Bacterial and virus infections may be made worse and use of steroids to suppress inflammation of infection is generally undesirable and must be accompanied by chemotherapy. Application is generally as hydrocortisone drops or subconjunctival injection.

Nephrotic Syndrome. An unpredictable minority of patients respond to anti-inflammatory steroids by diuresis, on commencing or on reducing or ceasing therapy. Substantial reduction in albuminuria may be achieved in some cases, with return of plasma protein to normal.

A Variety of Skin Diseases such as eczema, see chapter 27.

Acute Gout resistant to other drugs (p. 180).

Miscellaneous Diseases. In these, other lines of treatment should be tried first where they exist. Steatorrhœa, severe nasal allergy (topical application), "aphthous" ulcers in the mouth (suck a 2·5 mg. hydrocortisone tablet four times daily) (*9*), acute polyneuritis, toxic encephalitis, severe infective hepatitis, post-irradiation fibrosis, mumps orchitis, Hunner's ulcer of the bladder and many other diseases.

Guide to Further Reading on Corticotrophin and Adrenocortical Hormones

(*1*) Thorn, G. W., Nelson, D. H., and Renold, A. E. (1958). Current status of the treatment of adrenal disorders. *J. Amer. med. Ass.*, **168**, 2130.

(*2*) Lukens, F. D. W. (1954) (Editor). Medical Uses of Cortisone, including Hydrocortisone and Corticotrophin. Philadelphia: Blakiston.

(*3*) Germuth, F. G. (1956). The role of adrenocortical steroids in infection, immunity and hypersensitivity. *Pharmacol. Rev.*, **8**, 1.

(*4*) Romansky, M. J. (1959). Steroid therapy in systemic infections. *J. Amer. med. Ass.*, **170**, 1179.

(*5*) Witts, L. J. (1958). The effects of ACTH and corticosteroids in the alimentary tract. *In* Modern Trends in Gastro-enterology. 2nd series. Ed. F. A. Jones. London: Butterworth.

(*6*) Editorial (1959). Testing adrenocortical function. *Brit. med. J.*, (*ii*), 1160.

(*7*) Editorial (1958). Emotion, exercise, and the adrenal cortex. *Brit. med. J.*, (*ii*), 496.

(*8*) Editorial (1959). Arthritis and corticosteroids. *Brit. med. J.*, (*ii*), 1390.

(*9*) Cooke, B. E. D., and Armitage, P. (1960). Recurrent Mikulicz's aphthæ treated with topical hydrocortisone hemisuccinate sodium *Brit. med. J.*, (*i*), 764.

(*10*) Treatment of polyarteritis nodosa with cortisone: Results after three years. Report to the Medical Research Council by the collagen diseases and hypersensitivity panel (1960). *Brit. med. J.*, (*i*), 1399.

Chapter 6

HYPNOTICS, SEDATIVES, ANTICONVULSANTS

Drugs which Depress the Central Nervous System

The following terms are commonly used:—

Narcotic: any drug which depresses the central nervous system. The term is often used to include only general anæsthetics, hypnotics and opiates, or loosely to mean all drugs of addiction and therefore to include some convulsants (cocaine). This is a pity, as it tends to cause confusion.

Hypnotic: a drug to induce sleep.

General Anæsthetic: a drug used to induce easily controllable and reversible unconsciousness.

Sedative: a drug used to quieten a patient without sending him to sleep; although it may make him feel sleepy. A small dose of a hypnotic often suffices for this.

Tranquilliser: a drug used to quieten a patient. The ideal tranquilliser would allay pathological anxiety and nervous tension without altering any other cerebral functions; especially it would not cause sleepiness. It would also suppress mania and psychotic overactivity. The term "ataractic" is sometimes used. It is derived from a word meaning peace of mind.

Analgesics: relieve pain.

Anticonvulsants: prevent and suppress convulsions.

Drugs which induce abnormal states of mind are called *psychotomimetics* (p. 211). When they cause hallucinations the term *hallucinogen* may be used.

It is clear from the above vague definitions that the groups overlap. None is more indefinite than the tranquillisers which are a very heterogeneous group of substances. This group is quite arbitrarily considered to include only the more recently introduced substances and to exclude the barbiturates and other hypnotics, although these are invaluable as tranquillisers in practice. There is some justification for this because tranquillisers such as reserpine or chlorpromazine do not, even at high doses, induce the relatively harmless and readily reversible unconsciousness characteristic of hypnotics.

The tranquillisers and psychotomimetics are sometimes grouped as *psychotropic* drugs, *i.e.* drugs which affect the mind.

The Mechanism of Action of Cerebral Depressant Drugs is obscure and nothing can usefully be added to the remarks made about general anæsthetics. Much is known, but the knowledge cannot yet be synthesised into a coherent account of how the drugs act. Where relevant, additional information is given in the accounts of individual drugs.

HYPNOTICS AND SEDATIVES

These drugs will be described in approximate chronological order of their introduction, but the opiates are considered under analgesics although most are excellent sedatives or hypnotics.

Chloral Hydrate (1869)

Chloral hydrate was the first synthetic hypnotic to be introduced and was a welcome alternative to opium and alcohol. Chloral is a solid and is usually given orally in solution because it is so irritant to the stomach. Tablets evaporate and capsules are unwieldy. Its taste is unpleasant. As an alternative the less irritant chloralformamide may be given as a tablet. Chloral is readily absorbed from the intestine and induces sleep in about half an hour, lasting six to eight hours with little hangover. Chloral is metabolised chiefly in the liver and kidney. A principal metabolite is trichloroethanol, itself an effective hypnotic. The ultimate metabolites are excreted in the urine and reduce Fehling's and Benedict's solutions. There is no good evidence to support the commonly made statement that chloral is contra-indicated in cardiac disease, but it is dangerous in serious hepatic or renal failure, and may be bad for patients with peptic ulcer. It is especially widely employed at the extremes of life, in the elderly because barbiturates are inclined to cause confusion, and in children because there is a disinclination to use barbiturates owing to the ease with which poisoning occurs.

The hypnotic dose of chloral hydrate is 0·5 to 2 G. and of chloralformamide 1 to 3 G., orally. Chlorbutol is related to chloral hydrate; it often appears in proprietary medicines and has no particular merit.

Paraldehyde (1882)

Paraldehyde is an offensive, irritant, inflammable, but not explosive liquid. It is a safe and therefore valuable hypnotic but has a great disadvantage in addition to those mentioned above. A proportion (10 to 30%) is excreted unchanged in the breath, so that after taking it a patient may smell and indeed make a large room smell for 24 hours, though unconscious of it himself. When swallowed it acts in about 15 minutes and lasts four to eight hours. Hangover is usually trivial. Most of a dose of paraldehyde is metabolised in the liver and action may be prolonged in cases of liver disease. Paraldehyde is chiefly employed as an occasional hypnotic, especially in alcoholics, *e.g.* in delirium tremens, who tend to be tolerant of it unless they have hepatic cirrhosis. Addiction occurs. It is also used as a basal narcotic for surgery and as an anticonvulsant in status epilepticus, tetanus and eclampsia. The dose is 5 to 10 ml. by oral, i.m. or rectal administration although this can often be safely exceeded. When a large dose is given i.m. it is advisable to divide it between two sites to reduce the liability to chemical abscess formation. When given rectally it should be diluted to 10 times the volume of the dose with 0·9% sodium chloride solution. Paraldehyde is not self-sterilising. It decomposes, especially when subject to light and heat, when as much as 70% may become acetic acid. Deaths due to corrosive poisoning with acetic acid have occurred with old paraldehyde, so any stored for over six months should be discarded or at least tested for acidity before use.

Barbiturates (1903)

The development of organic chemistry in the late 19th century led to the testing on animals of many compounds in the search for an ideal hypnotic drug. Because urethane was known to be a hypnotic, although weak and unreliable, other urea derivatives were investigated. Derivatives of barbituric acid (malonyl urea) were found to be effective and in 1903 barbitone was introduced to clinical practice. Since then a huge number of barbiturates have been tested and many are used to provide depression of the central nervous system ranging from mild sedation to surgical anæsthesia. For practical purposes all depressant barbiturates have qualitatively similar actions; they differ only in the rate and method of disposal in the body and this has a bearing on their clinical use. In addition phenobarbitone and methylphenobarbitone differ in that their anticonvulsant effect is greater relative to the hypnotic effect. Barbiturates which are convulsants have also been made but have not found clinical use.

Like other cerebral depressants, barbiturates act on the higher centres first, the depression proceeding down the central nervous system. Death from overdose is due to respiratory depression.

After oral administration of a hypnotic dose sleep begins in about 20 minutes and lasts a variable time depending on the particular compound used. Some details about the most commonly used barbiturates are given in the table. The longer acting drugs are more slowly absorbed than the short acting, except for thiobarbiturates which are poorly absorbed and so are not used orally. The duration of action depends chiefly on the rate at which the drug is broken down in the body. The fate of the drugs is given in the table on p. 104.

Barbiturates are powerful anticonvulsants, injections of the soluble

The Commonly Used Barbiturates

Name	*Oral hypnotic dose*	*Duration of action*	*Fate in body*
barbitone (Medinal)	300–600 mg.	long more than 6 hours	excreted unchanged by kidney
phenobarbitone (Luminal)	30–120 mg.		20% excreted unchanged by kidney, 80% metabolised
methylphenobarbitone (phemitone)	60–200 mg.		
butobarbitone (Soneryl)	100–200 mg.	medium 3 to 6 hours	metabolised in the liver
amylobarbitone (Amytal)	100–200 mg.		
pentobarbitone sodium (Nembutal)	100–200 mg.		
quinalbarbitone sodium (Seconal)	50–200 mg.	short less than 3 hours	
cyclobarbitone (Phanodorm)	50–300 mg.		
hexobarbitone (Evipan)	250–500 mg.	ultra-short, used as i.v. anæsthetic	stored in the fat and metabolised in the liver
thiopentone sodium (Pentothal)	thiobarbiturates are not used orally		
thialbarbitone sodium (Kemithal)			

Sodium salts of most of those listed are available for parenteral use and are sometimes given orally, *e.g.* sodium amylobarbitone, up to 300 mg. orally.

sodium salts of all forms being used for urgent treatment, and oral phenobarbitone and its methyl derivative in the routine control of epilepsy by oral therapy. Those barbiturates which are suitable, chiefly by reason of their duration of action, for use as general anæsthetics are discussed on p. 132. Analgesia is not produced by hypnotic doses and use of these drugs in patients suffering from pain without concurrent administration of an analgesic is liable to cause restlessness and mental confusion. Barbiturates reduce, and eventually abolish, sensitivity of the respiratory centre to carbon dioxide so that the stimulus to respiration becomes hypoxia, just as it is in patients with severe emphysema and excessive carbon dioxide retention. In either case sudden relief of hypoxia by administration of oxygen can result in respiratory failure, as the centre is suddenly deprived of its driving stimulus. This may be of practical importance in the management of barbiturate poisoning, but should not prevent oxygen being given as it probably does not happen often. Barbiturates should be used with caution, if at all, in patients with respiratory depression. There is synergism with other central nervous system depressants and an ordinary hypnotic dose can be fatal in patients who have taken a lot of alcohol.

Hypnotic doses have no significant effects on circulatory, renal, hepatic or gastro-intestinal systems.

Barbiturates, especially barbitone, may induce attacks in patients with latent porphyria.

No attempt has been made to include all the available barbiturates in this account. As hypnotics there is nothing to choose between a considerable number of compounds in the medium and short-acting group. A satisfactory pair would be butobarbitone and quinalbarbitone. As a sedative phenobarbitone is satisfactory and widely used; it is too long-acting to be very useful as a hypnotic. Barbiturates are also used for prolonged narcosis and other psychiatric purposes. The choice of drugs in convulsive states is discussed on p. 115. For intravenous anæsthesia no drug has been shown to be superior to thiopentone. For oral use the barbiturate or its soluble sodium salt can be used, it matters little; but for parenteral administration a sodium salt is required. Soluble barbiturates may be injected i.m. or s.c., when the dose is similar to that given orally. For i.v. injection the drug is given slowly and the dose judged by results. It is dangerous to give long-acting barbiturates i.v.

The toxic effects of barbiturates are almost entirely those of overdose, coma and respiratory and circulatory failure. Hypersensitivity reactions occur occasionally, particularly with phenobarbitone, skin reactions being the most common, but severe fatal allergic reactions have rarely been recorded.

On the whole barbiturates have shown themselves very satisfactory drugs, their frequent employment as suicidal agents being an index of their widespread use, rather than of any particularly undesirable property.

Bromide (1857)

Because iodides were useful in the treatment of syphilis and goitre, bromide was tried in the same conditions and its sedative effect accidentally revealed.

In 1857, at a discussion on the treatment of epilepsy, Sir Charles Locock mentioned that he had tried potassium bromide on 15 epileptics and "cured" 14 of them. He had been led to try it because of his belief that sexual excess could cause epilepsy and because he had heard that bromide could induce sexual impotence. He did not further publicise this discovery, but its use became widespread and bromide remained the only effective anti-epileptic treatment until the introduction of phenobarbitone in 1912.

Bromide depresses the whole central nervous system. It reduces motor restlessness and causes sedation with minimal drowsiness in therapeutic doses. Larger amounts cause mental depression, lassitude and sleepiness. It is an effective anticonvulsant but has been almost completely supplanted by more modern synthetic drugs both for this and as a sedative. Bromide is not an analgesic.

Bromide is readily absorbed from the alimentary tract and is distributed throughout the body, almost entirely in the extracellular fluid. It is treated by the body just like chloride and so, if the intake of bromide is high and that of chloride low, bromide will replace chloride in steadily increasing amount until toxic levels are reached. Since a substantial amount of chloride must be replaced before sedation occurs many grams would be needed to achieve this with a single dose, so that it is evident that casual administration of two or three grams occasionally is irrational, as it cannot have any effect at all other than as a placebo. Bromide is thus essentially a substance for chronic medication, it being necessary to build up the concentration in the body to the required level over a few days. Effects are obviously dependent on the patient's chloride intake since both substances are treated identically, so that the dose required is rather unpredictable.

Sodium or potassium bromide are usually employed, and 2 to 4 G. a day will give sedation in a few days. Toxicity may appear at a blood level of 100 mg./100 ml. (12·5 m. Eq. litre) and symptoms are very common at 150 mg./100 ml. (19 m. Eq. litre). If no steps are taken to hasten bromide excretion and the sodium chloride intake is average the blood level falls by about 50% in four weeks, so that a patient may be left with toxic effects for some weeks after leaving off the drug. Excretion may be hastened by a high daily intake of fluid (4 litres) and chloride (5 to 10 G. sodium chloride above what is in the diet). Diuretics (chlorothiazide or organic mercurials) are also valuable and hæmodialysis may be needed in extreme cases. If it is undesirable to give sodium in a particular patient (cardiac failure), ammonium chloride may be substituted, but the ammonium ion is undesirable in hepatic disease.

Bromide intoxication (bromism) declares itself with psychotic states of all kinds, but chiefly depression and irritability, although excitement may occur. It is dangerous to use more sedative for this excitement, although it may have to be done. Tremors and incoordination with depressed reflexes occur. Rashes, commonly acneiform, on the face and upper half of body are usual. Increased mucus secretion from mouth, nose and eyes causes the patient to appear to have a "cold". Headache, anorexia, foul breath, indigestion and constipation occur. Confirmation of the diagnosis is obtained by measuring the blood bromide level as well as from the history.

Bromism commonly occurs insidiously and the symptoms may be attributed to the disease for which the sedative is given, sometimes with the result that the dose has been increased. Prescriptions for bromide can be renewed indefinitely by the patient who can also obtain bromide in a variety of proprietary medicines. Failure to diagnose bromism is often due to failure to think of it. Bromide is obsolescent because of the difficulty in handling it with benefit and without risk of poisoning and because barbiturates seem to be able to do virtually all that bromide can. It is still used in resistant cases of epilepsy and occasionally to control nervous tension with restlessness.

Non-barbiturate Hypnotics

Methylpentynol (Oblivon) is a liquid taken orally in a capsule; the hypnotic dose is 250 to 500 mg. It begins to act in about half an hour and rarely causes hangover as it is fairly short acting (four hours) although there may be an unpleasant taste on belching the next day. It is useful as a pre-operative sedative for children and in dentistry, as its actions are mild and brief. Dermatitis has been reported, and so has death from overdose.

Glutethimide (Doriden) is related to the barbiturates; taken orally (250 mg. to 500 mg.) it acts for about six hours.

Methyprylone (Noludar) (200 to 400 mg. orally) acts for about six hours.

Carbromal is a useful safe, mild hypnotic (0·3 to 1 G. orally) which acts for about four hours. Rashes, confusional states and addiction have been reported and bromism can occur with prolonged use, although bromide is not responsible for its hypnotic utility. Carbromal is sometimes combined with a barbiturate, *e.g.* Carbrital, which contains carbromal and pentobarbitone.

Bromvaletone (oral dose: 300 to 600 mg.) is similar to carbromal. Both drugs are urea derivatives. Mixtures of carbromal and bromvaletone are sometimes used, *e.g.* Persomnia.

Meprobamate has been found to be an effective hypnotic for some patients. It is described under tranquillisers.

Promethazine is a useful long-acting hypnotic in children. It is described under antihistaminics. It potentiates barbiturates as do most other phenothiazine compounds. Trimeprazine (Vallergan) is similar.

Thalidomide (Distaval) (hypnotic oral dose: 100 to 200 mg.). This substance, probably by virtue of insolubility, appears to be unable to induce deep coma in man. Nor has it been possible to find an oral lethal dose in animals. It has been reasonably suggested that thalidomide is especially suited for use as a sedative (25 mg., twice a day) and hypnotic in patients in whom there is particular reason to fear a suicidal attempt. Hangover and rashes occur and the drug has a very weak antithyroid effect which is claimed to be of no clinical significance.

Sulphonal and its Derivatives are toxic to the liver, kidney and blood and so are obsolete.

Apronal (Sedormid) is a urea derivative that is famous for causing thrombocytopenic purpura, for which reason it is deservedly obsolete.

There are many more hypnotics available, but none will accomplish anything that cannot be done by a selection of those described above.

General Remarks on the Use of Hypnotics and Sedatives

Chloral hydrate and barbiturates are likely to be satisfactory as hypnotics in the majority of patients, and the newer hypnotics only need to be used in cases where, after appropriate efforts to find a suitable dose of those drugs, the results are still unsatisfactory. Hangover is common with all hypnotics and the "short-acting" barbiturates are by no means as incapable of causing it as that designation implies. Quinalbarbitone and butobarbitone are probably capable of doing all that is required, but the choice is not critical. In treating insomnia there is a great deal more involved than simply giving a drug. When drugs are used the choice will be influenced by whether the patient has difficulty in getting to sleep or wakes early. Where sleeplessness is due to pain an analgesic is essential in addition. In some cases the fact that alcohol has synergistic effects with all hypnotics will have practical importance. In general, patients should not take the drugs more than 20 minutes before getting into bed, for obvious reasons.

Elderly people and those in pain may become confused with hypnotics and an occasional patient becomes excited. Sometimes patients have nightmares after a particular drug. Irritant drugs (chloral, paraldehyde) are obviously unsuitable in patients with peptic ulcer.

In cases where it is especially desired to avoid any respiratory depression, *e.g.* in severe asthmatics or in head injury, chloral hydrate and paraldehyde are preferable to the barbiturates. Chronic sedation is achieved with lower doses of hypnotics (25 mg. of phenobarbitone or 100 mg. of amylobarbitone are commonly used) two or three times a day and are preferable to bromides. Chronic sedation is commonly accompanied by constipation.

Although children are tolerant of barbiturates they are seldom used as hypnotics for them because of the facility with which poisoning occurs in the home. A fatal dose of chloral or promethazine, both irritant substances, is less easily consumed and retained.

Addiction is known to occur with all the older and most of the newer hypnotic drugs. There can be little doubt that there will be reports of addiction to all such drugs in due course, for to some mentally abnormal people mere alteration of consciousness is a desirable end. The problem of addiction to these drugs is very small compared with the morphine derivatives. Tolerance to hypnotics occurs, but is relatively slight. True addiction requires very heavy doses over many months and probably does not occur at all if what are generally recognised as therapeutic doses are not exceeded. Addiction is accompanied by signs of mental and physical deterioration, *e.g.* abnormal behaviour, ataxia, tremors. Addiction to bromides does not occur. The characteristics of addiction are discussed on p. 183. Sudden withdrawal of any of these drugs from an addict is extremely dangerous as convulsions and psychotic behaviour may result.

Poisoning by Hypnotic Agents

This problem will be discussed as barbiturate poisoning, but most remarks apply to other hypnotics. Some cases of barbiturate poisoning result from a patient taking a large dose, going to sleep and then waking after a short time in a confusional or amnesic state and taking a second dose. It is not known how often this occurs, but the sequence is not seldom proposed at coroners' inquests.

The treatment of the comatose patient poisoned with barbiturate consists in keeping him alive until his body has disposed of the drug, and preventing complications such as electrolyte imbalance, circulatory collapse and pneumonia. In addition to putting into practice the general principles stated on pp. 429–430 this involves chiefly attention to respiration and circulation. Full oxygenation is vital.

Many patients do not need any analeptic drugs at all. There is a marked tendency to overtreat patients with barbiturate poisoning; the temptation to interfere unnecessarily must be resisted. If a pharyngeal reflex is present and respiration is adequate to preserve oxygenation, then no respiratory stimulants are required. There is no indication for attempting to wake the patient up.

Death from respiratory failure may be prevented by artificial respiration or by stimulating respiration with drugs. If the facilities and skill are available it is probable that the results of intermittent positive pressure artificial respiration cannot be surpassed. If it is decided to use drugs when the respiration becomes inadequate, then there is a wide choice: nikethamide, leptazol, amphetamine, bemegride and picrotoxin. Caffeine, as a retention enema of coffee, is a traditional emergency remedy. Unfortunately no scientific comparison of the merits of any one régime with another has proved possible. Probably the most important thing is to decide what is going to be done and to do it without repeatedly having second thoughts and putting them into practice so that the picture becomes confused by the polypharmacy that is characteristic of indecision.

When it is wished to stimulate respiration 5 ml. of 10% leptazol solution may be given slowly i.v., and repeated as necessary, which may be about every 20 to 30 minutes. For longer action amphetamine, 10 to 20 mg. i.v., or i.m., may be given, especially if the blood pressure is unduly low. These two drugs may be used in combination. Excess of amphetamine, *i.e.* more than 300 mg. in 24 hours, may cause fatal cardiac arrhythmia. Equally good, or bad, results can be achieved with the other drugs mentioned above. The dose of nikethamide required may be high, 2 to 10 ml. i.v. of the usual 25% solution, repeated as needed every 20 to 30 minutes. Bemegride, 50 mg. i.v. every 5 to 10 minutes, is a fashionable respiratory stimulant but there is no convincing evidence that it is superior to leptazol. Picrotoxin, 6 mg. i.v. every 30 to 40 minutes, may have a delayed onset of action and so the interval between doses should not be reduced. Patients given analeptics should be watched carefully for early signs of overdose, twitching of the face or extremities, which can occur before any improvement in respiration, in which case administration should stop.* Antimicrobial chemoprophylaxis, usually by penicillin, is generally employed if the patient is unconscious more than 12 hours.

As might be expected, attempts to determine the merits of a treatment are frequently made by comparing published mortality rates. So intrinsically variable a condition is poisoning, especially suicidal poisoning, that it is important to be wary of any such claims. That figures based on less than several hundred cases are useless is made clear by the fact that in one hospital there were 134 consecutive recoveries amongst patients comatose on admission to hospital and then three deaths in the next five cases (*2*).

A genuinely specific barbiturate antagonist, that is a drug acting by substrate competition, is much needed, and development of such a substance should not be a very difficult matter for the modern pharmacological chemists. It would be a great deal more useful than merely adding drugs of little merit to the already unnecessarily long list of available hypnotics.

DRUGS USED AGAINST CONVULSIONS AND OTHER FORMS OF EPILEPSY

Bromide (1857) was the first effective anti-epileptic drug, but is now virtually obsolete. When phenobarbitone was introduced in 1912 it was found to control patients resistant to bromides and to be far superior to barbitone which had been available since 1903. It became clear that minor differences in chemical structure were significant and that, in the barbiturate series, there was prospect of separating the hypnotic from the anticonvulsant effects. But these possibilities could not be exploited fully without suitable animal experimental techniques. Such techniques were developed in the 1930's, and resulted in the introduction of phenytoin in 1938 (*1*). Phenytoin is chemically related to the barbiturates. Since then many drugs have been discovered by the same techniques, but phenobarbitone and phenytoin remain the most useful drugs in the treatment of major epilepsy.

---

* The above intervals between doses are only a guide to commencing therapy: the drugs are "titrated" against respiratory depression as clinical judgment counsels.

The Production and Prevention of Experimental Convulsions

In the laboratory, convulsions are induced in animals, usually rats or mice, by electric shock of various kinds and by the injection of drugs such as leptazol. Fits and abnormal electroencephalographic patterns can be produced, which resemble the three principal kinds of epilepsy, major epilepsy (grand mal), minor epilepsy (petit mal) and psychomotor epilepsy. While nobody supposes that such tests exactly represent clinical epilepsy, they have resulted in the discovery of a number of useful anticonvulsants. The order of clinical efficacy of drugs is not perfectly reproduced if they are ranked by means of animal laboratory tests, although there is some correlation.

Epilepsy

Epilepsy has never been more accurately defined than by Hughlings Jackson a long time ago when he said it was a sudden, excessive and rapid discharge of grey matter of the brain. Moreover, he early recognised that most (if not all) forms of epilepsy have a focal origin, the form of the seizures depending on the site of the focus in the brain, the regions to which the discharge spreads, and the effects of post-ictal paralysis of these regions. Although the exact relationship of the abnormal and excessive excitation to normal neuronal activity is not yet established, it has long been known that any general depressant of nervous activity (*e.g.* a general anæsthetic) will diminish or abolish epileptic activity. Anticonvulsants are drugs which inhibit epileptic discharge with minimal general depressing or hypnotic effect. Animal experiments suggest that these drugs act less on the activity of the epileptogenic focus than on the spread to normal grey matter. There is no evidence that such drugs have any prophylactic value in preventing an area of brain damage (*e.g.* after a head injury) from becoming epileptogenic, although phenobarbitone is commonly given after severe cerebral trauma.

Anticonvulsant Drugs

The principal anticonvulsant drugs and their more prominent side-effects are set out in the table, p. 113. In general, dosage is increased weekly, to allow each dose to cumulate to a steady level before adding more and because maximum therapeutic effect takes time to develop.

Other anticonvulsant drugs include benzchlorpropamide (Nydrane) for grand mal and aloxidone (Malidone) for petit mal. Phenacemide is a drug of last resort in all forms, especially psychomotor; it is too toxic for general use (liver damage, blood dyscrasias and psychotic states).

In addition acetazolamide, a carbonic anhydrase inhibitor (p. 310) may be effective in petit mal. It can be added to existing drug therapy. Myoclonic epilepsy is ordinarily very resistant to treatment but mephenesin and mephenesin-like drugs (p. 206) can be effective in very high doses.

All anticonvulsants should be used cautiously in the presence of renal or hepatic failure which may potentiate them.

The Drug Treatment of Epilepsy

As more effective anticonvulsants become available the possibility of dramatic advances naturally becomes less, so that it is important to be able to detect even small improvements in therapeutic effect. This means that therapeutic trials have to be designed and conducted more carefully and accurately than before. It is, for example, of little interest to know that a new drug can control, say 50% of epileptics presenting at a clinic, for these might be adequately controlled by existing drugs without any greater toxicity. It is important to try new drugs on patients resistant to existing therapy.

There are four important principles in the treatment of epilepsy:—

1. Treatment of causative factors, *e.g.* cerebral neoplasm.
2. Avoidance of precipitating factors, *e.g.* alcohol, excitement.
3. Anticipation of natural variations, *e.g.* fits may occur only at night or shortly after waking.
4. Anticonvulsant drugs.

Throughout this book little is included about therapy other than drugs, but this does not mean that drugs are necessarily the most important feature of the treatment of any disease. The principles of drug therapy of epilepsy are simple, have been well stated by Putnam (2), and illustrate many of the principles of drug therapy in general:—

1. Relatively well-known and non-toxic drugs should be preferred to dangerous or untried ones, which should only be added if the former have failed.

2. The maximum tolerated dose should be found for each drug, *i.e.*

The Principal Anticonvulsant Drugs

Chemical group and non-proprietary name (Proprietary name)	*Approx. total daily oral dose (given in 2–4 doses)*	*Type of epilepsy against which drug is effective*	*Remarks and Toxicity*
Barbiturates and primidone			
phenobarbitone (Luminal)	100–400 mg.	grand mal	A drug of 1st choice. Sleepiness, occasional rashes
methylphenobarbitone, phemitone (Prominal)	100–400 mg.	grand mal	As above
metharbital (Gemonil)	100–600 mg.	grand mal ? petit mal	As above
primidone (Mysoline)	250–2000 mg.	psychomotor grand mal ? petit mal	Sleepiness, nausea, ataxia, which often disappear after first few doses. Megaloblastic anæmia which responds to folic acid. Closely related to phenobarbitone
Hydantoins			
phenytoin sodium (Epanutin, Dilantin)	300–600 mg.	grand mal psychomotor	A drug of 1st choice. Hyperplasia of gums, specially in children. Ataxia, headache, tremors, rashes and blood dyscrasias, incl. megaloblastic anæmia which responds to folic acid
methoin (Mesontoin)	100–600 mg.	grand mal psychomotor	Ataxia, tremors, blood dyscrasias, no gum hyperplasia
Oxazolidinediones			
troxidone (Tridione)	600–1200 mg.	petit mal	A drug of 1st choice. May make grand mal worse and should be combined with phenobarb. in cases with both petit and grand mal. Photophobia, day blindness and dazzle; nephrotic syndrome, hiccough, blood dyscrasias, rashes
paramethadione (Paradione)	600–1200 mg.	Petit mal, slightly in other forms	As above but less photophobia
Miscellaneous			
phensuximide (Milontin)	1–3 G.	petit mal psychomotor	Sleepiness, headache, vomiting, rashes
bromide	300–1000 mg.	grand mal	Used only when others fail, see pp. 105–107

the dose should be increased until symptoms of overdose are produced and then it should be reduced slightly. The best therapeutic effect is usually only obtained near the toxic dose.

3. Unless a drug under trial is obviously useless it should not be stopped until the next drug to be tried is being given in reasonable dose. Sudden withdrawal of an effective drug may result in status epilepticus. If sudden withdrawal of an effective drug is necessary because of toxicity, a very substantial dose of another drug should be given at once.

4. This trial of drug after drug should be continued until the epilepsy is controlled, or until there are no more drugs to try. Up to three months may be needed to try a drug thoroughly in an individual patient.

5. In cases where fits are liable to occur at a particular time of day, dosage should be adjusted to achieve maximal drug effect at that time.

Amphetamine may be used to counteract drowsiness due to the drugs without making the fits worse, but it is not a very good principle to oppose one drug with another if it can be avoided, for drug effects seldom exactly cancel each other out. It is naïve to imagine that amphetamine versus phenobarbitone equals normality.

It is doubtful whether any epileptic is ever the better for taking more than three anticonvulsant drugs at a time, and he is seldom the better for more than two. Chlorpromazine may make epilepsy worse.

In patients who are not relieved by any combination of drugs tried in the usual way, intensive anticonvulsant therapy in hospital with phenytoin (4 G. total per day for four days) can be tried. The patient may be too sleepy to eat or drink on this dose and may need fluid and glucose by vein. Very careful supervision is vital, and the treatment is not to be lightly undertaken. After the course the patient may respond to ordinary anticonvulsant dosage. Dehydration, by withholding fluids, sometimes helps in resistant cases. Although pregnancy may make epilepsy worse it often does not, and routinely increasing anticonvulsants in pregnancy is not necessary unless the patient's response is known to be unfavourable; nor is it necessary to increase medication before surgery.

Results of Drug Treatment of epilepsy may be summed up thus. About a third of patients are completely relieved of fits, one in five of whom may be able to give up drugs after three years, without recurrence. About a third are partially relieved and about a third (probably rather less) are not benefitted at all.

Choice of Drugs in Epilepsy

The doses and toxic effects of the principal drugs used in epilepsy are listed in the table on p. 113. The chemical structures of the three main groups of anticonvulsants, barbiturates, hydantoins and oxazolidinediones are all related.

Grand Mal. Phenobarbitone and phenytoin are the drugs of choice. A patient may begin treatment with 30 mg. phenobarbitone orally, two or three times a day. If the patient tends to have his fits at any particular time of day then medication should naturally be heaviest then. Some patients who have fits soon after rising in the morning may be advised to take a dose on waking and to stay in bed for at least a further 15 minutes. The dose of phenobarbitone may be increased up to a total of about 200 mg. in a day, at which dose sleepiness will probably be intolerable.

If control is incomplete then phenytoin may be added, 100 mg. three times a day and increased up to a total of about 600 mg. a day. If control becomes complete it may be possible to reduce the dose of phenobarbitone or even to withdraw it.

If control is still incomplete, primidone and then other drugs can be tried in a similar fashion. If a drug is useless it can be withdrawn suddenly, if not, withdrawal *must* be gradual.

Petit Mal (and physiologically related seizures such as generalised myoclonus). Troxidone is the drug of choice, 300 mg. is given two to six times a day increasing to the maximum tolerated dose. The drug of second choice is paramethadione.

Phenobarbitone can make petit mal worse. Amphetamine often helps. Acetazolamide can be tried in resistant cases.

Psychomotor Attacks. Primidone is usually best, although toxic effects are common with the first few doses, after which they often disappear. Phenytoin may be useful and so may phensuximide.

Duration of Anti-epileptic Drug Therapy

It is essential that full drug therapy be continued for at least two years after the last fit. Those who are by nature cautious would put it at three years, after which time the drugs can be withdrawn gradually over a period of weeks. If another fit occurs then a further two to three-year period is necessary before another attempt is made to withdraw therapy.

Status Epilepticus

There is no agreement on the best drug treatment of this serious condition. It is a matter of urgency to stop the fits. The danger of causing serious respiratory depression is substantial in a patient whose respiratory centre is already depressed as a result of the convulsions. Perhaps the first choice should be phenobarbitone (200 mg., i.m.) repeated as necessary. Paraldehyde (5 to 10 ml., i.m.) will also serve. Barbiturates given i.v. are dangerous, but may be needed in an emergency and should be injected very slowly indeed.

It is better to use an anticonvulsant which is familiar than an unfamiliar drug chosen on hypothetical grounds. In resistant cases lignocaine i.v. has proved successful (p. 145). Inhalation anæsthetics may be used in emergency to gain time to arrange less drastic therapy.

Fits in Children

Fits in children are treated as in adults, but children may respond differently to the drugs and become irritable, especially with phenobarbitone. If febrile convulsions have occurred, phenobarbitone (or phenytoin) should be given whenever the child subsequently becomes febrile. This is important between the ages of 1½ and 3 years. There is a strong familial tendency to febrile convulsions and it has been proposed that if a child has them, its siblings should receive similar prophylactic medication during the most dangerous period (1½ to 3 years). If convulsions only occur when the child is febrile there is probably no need for continuous anticonvulsant medication. Sometimes convulsions occur at the onset of fever and so cannot be forestalled. Continuous medication can then be given if they are at all frequent, but opinions on just when to embark on continuous medication in children who are dubiously epileptic are very variable.

TETANUS

Whilst only the pharmacology of the convulsions can be strictly considered appropriate to this book, the practical immunological aspects of tetanus are also discussed as they form a perennial clinical problem.

It should be said at once that the best treatment of tetanus lies in active immunisation, a safe and effective measure. It consists of three injections of 1 ml. of toxoid, the second six to 12 weeks after the first and the third six to 12 months after the second, followed by a booster dose every five years.

Passive immunisation is troublesome and carries substantial morbidity and a small and often dramatic mortality, for it involves the use of foreign protein. It is also unreliable in some circumstances described below. In addition some 30% of cases of tetanus show no definite wound to which the disease can be attributed and a number of cases occur from extremely trivial wounds. Such cases naturally cannot be protected passively by antitoxin, for they cannot be foreseen.

The Prophylaxis of Tetanus

When a patient has a wound that requires prophylaxis against tetanus (deep wounds, wounds with much devitalised tissue, septic wounds or wounds contaminated with soil) the following procedure may be adopted:

1. Enquiry is made into the immunity status of the patient. The most likely result is that either the patient has never been actively immunised, that he probably has been immunised in the past but that it is more than five years ago or that it is quite impossible to determine whether he has ever been actively immunised or not. In all these cases the patient should be considered non-immune.

2. Actively immune patients are those who have had three injections of toxoid at the proper intervals, and a booster dose of toxoid every five years after the initial course. A booster dose of 1 ml. of toxoid following a wound is indicated in the actively immune if the last toxoid injection was given more than 18 months previously. Within 18 months no booster dose is required.

3. Non-immune patients require passive immunisation with anti-tetanus serum (A.T.S.). The procedure is as follows:—

a. Enquiry is made into any history of allergy or previous administration of horse serum, for such patients are more likely to show hypersensitivity to the serum. Those who have had horse serum before may destroy it rapidly in the body and so not receive any protection from a subsequent dose; a cogent reason for active immunisation of *all* who have ever had horse serum for any reason (*6*).

b. If there is no history of allergy and the patient has never had horse serum before, a test dose of 0·2 ml. s.c. of the antitoxin to be used is given (the intradermal test is unreliable, giving both false positives and false negatives; skin sensitivity does not necessarily reflect systemic sensitivity). Adrenaline: 1 : 1,000 should be immediately available to abort any serious reaction. If in 30 minutes there have been no general symptoms, 1,500 or 3,000 International Units (I.U.) are given s.c. or i.m. If a patient has a history of allergy or has had horse serum before, the test dose should be 0·2 ml. of a 1 : 10 dilution of antitoxin in sterile water, followed, if there is no reaction in 30 minutes, by 0·2 ml. of undiluted toxin and then the procedure for the non-allergic patient.*

c. Ideally, arrangements should be made for a course of active immunisation.

The prophylactic dose of antitoxin (or toxoid) is the same for adults and children.

4. If a general reaction occurs to the test dose of the serum and it is desired to continue with administration of the full dose, the procedure described below under the treatment of tetanus is used. It may however be considered that the risk of serum reaction exceeds the risk of developing tetanus from the wound. A course of penicillin or tetracycline (not streptomycin) would then be reasonable as a preventive measure, but

---

* If there is good reason to expect serum hypersensitivity the patient's skin should be pricked through a drop of undiluted antitoxin (with saline control) and observed for local or general reaction before any injection is made.

would have to last until the wound was healed and symptom-free to cover the whole period of risk, for the spores are unaffected by the antibiotics.

It is quite impossible to dogmatise on which course should be adopted; obviously the severity and degree of contamination of the wound will play a large part in deciding whether the antitoxin should be given in the face of hypersensitivity.

The treatment of hypersensitivity reactions is described on p. 445.

5. If a wound is severe and danger from infection is considered to be prolonged beyond a week, antitoxin may be given weekly. To use longer intervals involves the risk of inducing anaphylaxis as well as low antitoxin blood levels.

The Treatment of Tetanus

There are five principal aims of treatment:—

1. To neutralise with antitoxin any bacterial toxin that has not yet become attached irreversibly to the central nervous system.
2. To kill the tetanus bacteria by chemotherapy.
3. To control the convulsions.
4. To prevent intercurrent infection (usually pulmonary).
5. To prevent electrolyte disturbances and to maintain nutrition.

It is usual to give adults a large dose of antitetanus serum, say, 200,000 I.U., but so much may be quite unnecessary. There are no reliable data on this point. This dose will provide high blood levels which outlast the disease unless the patient has had horse serum before, when he may destroy injected antitoxin in a few hours. There is evidence from animals that antitoxin given i.v. has greater protective value than when given i.m., but it is also more likely to cause anaphylaxis. A test dose should be given s.c. and may consist of 0·2 ml. of the antitoxin to be used. Even this can, rarely, cause death and some would use less and take the risk of missing a positive reaction (a more concentrated antitoxin is used for therapy than for prophylaxis). The test is positive if there are systemic symptoms. 30 minutes later, if there has been no reaction, 100,000 I.U. may be given i.m. and one hour later if there has been no reaction 100,000 I.U., i.v. If there is a reaction to the test dose in a patient with tetanus, the treatment of the sensitivity reaction (p. 445) should include a large dose of an antihistaminic, say diphenhydramine 50 mg. orally or 25 mg. i.m. After waiting until all symptoms of the hypersensitivity reaction have subsided and the blood pressure is normal (four to six hours) the same test is repeated. If there is no reaction, double the dose is given in 30 minutes and so on stepwise, doubling the dose each 30 minutes if the previous dose has produced no reaction, and reducing it slightly if it has, always allowing a reaction to subside before giving another dose. Adrenaline 1 : 1,000 should be at hand. Probably reactions can be prevented by hydrocortisone, i.v., but unfortunately there are no reliable data in man, nor on whether anaphylaxis may be prevented by anæsthetisation as is the case in animals. A recurrence of anaphylaxis within a few hours of an attack is unlikely.

In the unlikely event of an actively immunised person getting tetanus an injection of toxoid may be given at the same time as the antitoxin but not at the same site.

Chemotherapy with penicillin or tetracycline is effective against Cl. tetani and so will stop further production of toxin. It is often continued as prophylaxis against pneumonia but there is no certainty whether it is better to do this and risk pneumonia from antibiotic-resistant organisms or to stop the antibiotic after the wound has healed and start it again if infection occurs. In any case a severe wound may require prolonged chemotherapy, so that this problem does not always arise.

Convulsions may be controlled by barbiturates, paraldehyde or bromethol. All have the disadvantage that adequate dosage may lead to loss of consciousness for long periods and so promote respiratory failure and pneumonia. Chlorpromazine and mephenesin control convulsions without causing loss of consciousness, but may fail in the most severe cases. An excess of chlorpromazine may make the convulsions worse, probably by stimulating the brain stem reticular formation.

The dosage and route of administration can only be decided when confronted with the patient. A régime which should control convulsions of any severity would be chlorpromazine 100 mg. 4 to 6-hourly with sodium amylobarbitone i.m. or s.c. or i.v. in addition as required. It may be impossible to avoid abolishing consciousness at times.

An alternative is to paralyse the patient with tubocurarine or gallamine (on theoretical grounds these are probably preferable to depolarising agents) and provide artificial respiration. This treatment requires skill and much equipment, with facilities for measuring blood pH, electrolytes and gases. Unfortunately this limits its applicability, particularly in the countries where tetanus is common, so that it is especially difficult to know whether results are superior to the more conservative anticonvulsant régimes. Only a large-scale clinical trial can decide this point. Treatment by paralysis should only be used at present in very severe cases, and these are a minority. Unfortunately it is not easy to know which cases are going to become severe.

Anticonvulsant therapy may be needed for two weeks or more and so attention to nutrition and body electrolytes are vital right from the start. Nursing care, in avoiding convulsions and pneumonia, is at least as important as drug therapy.

An attack of tetanus does not confer immunity and as the patient will have had horse serum he should be actively immunised.

Guide to Further Reading

On Hypnotics and Sedatives

(*1*) Plum, F., and Swanson, A. G. (1957). Barbiturate poisoning treated by physiological methods. *J. Amer. med. Ass.*, **163**, 827.

(*2*) Locket, S. (1956). Barbiturate antagonists. *Proc. roy. Soc. Med.*, **49**, 585.

(*3*) Isbell, H., *et al.* (1950). Chronic barbiturate intoxication, an experimental study. *Arch. Neurol. Psychiat.* (Chicago), **64**, 1.

(*4*) Fraser, H. F., *et al.* (1958). Degree of physical dependence induced by secobarbital or pentobarbital. *J. Amer. med. Ass.*, **166**, 126.

On Anticonvulsants

(*1*) Merritt, H. H., and Putnam, T. J. (1938). A new series of anticonvulsant drugs tested by experiments on animals. *Arch. Neurol. Psychiat.* (Chicago), **39**, 1003.

(*2*) Putnam, T. J. (1958). The choice of an anticonvulsant. *In* Drugs of Choice, 1958-1959. Ed. W. Modell. St. Louis: Mosby.

On Tetanus

(*1*) Wright, G. P. (1958). The use of ATS in the treatment and prophylaxis of tetanus. *Proc. roy. Soc. Med.*, **51**, 997.

(*2*) Parish, H. J., Laurent, L. J. M., and Moynihan, N. H. (1957). Notes on prevention of tetanus in injured persons. *Brit. med. J.*, (*i*), 639.

(*3*) Laurence, D. R. (1958). The pharmacology of tetanus. *Proc. roy. Soc. Med.*, **51**, 1000.

(*4*) Adams, E. B. (1958). Clinical trials in tetanus. *Proc. roy. Soc. Med.*, **51**, 1002.

(*5*) Smith, A. C. (1958). The treatment of severe tetanus by paralysing drugs and intermittent pressure respiration. *Proc. roy. Soc. Med.*, **51**, 1006.

(*6*) Kind, L. S. (1957). Prophylactic value of tetanus antitoxin in mice previously injected with horse serum. *Brit. med. J.*, (*i*), 408.

Chapter 7

ANÆSTHETICS, NEUROMUSCULAR BLOCKING AGENTS, LOCAL ANALGESICS

ANÆSTHETICS

UNTIL the mid-19th century such relief of pain as was possible during surgery was achieved with natural substances such as alcohol, opium, hyoscine, cannabis indica and occasionally by concussion or suffocation. Modern anæsthesia began in the 1840's when the long-known substances nitrous oxide, ether and chloroform were introduced as anæsthetics in rapid succession.

The details surrounding the first use of surgical anæsthesia make unedifying reading at times, for there were bitter disputes on priority of discovery following an attempt to take out a patent for ether.

Sir James Simpson, who first used chloroform in man, heard of the initial trials of ether in 1846 and wrote,* "It is a glorious thought, I can think of naught else." Just before his death in 1870 he summarised the chief events of the introduction of anæsthesia in the U.S.A. "It appears to me that we might correctly state the whole matter as follows: (1) That on the 11th December, 1844, Dr. Wells had, at Hartford, by his own desire and suggestion, one of his upper molar teeth extracted without any pain, in consequence of his having deeply breathed nitrous oxide gas for the purpose, as suggested nearly half a century before by Sir Humphrey Davy.

"(2) That having with others proved, in a limited series of cases, the anæsthetic powers of nitrous oxide gas, Dr. Wells proceeded to Boston to lay his discovery before the Medical School and Hospital there, but was unsuccessful in the single attempt which he made, in consequence of the gas-bag being removed too soon, and that he was hooted away by his audience, as if the whole matter were an imposition, and was totally discouraged.

"(3) That Dr. Wells' former pupil and partner, Dr. Morton of Boston, was present with Dr. Wells when he made his experiments there.

"(4) That on the 30th September, 1846, Dr. Morton extracted a tooth without any pain, whilst the patient was breathing sulphuric ether, this fact and discovery of itself making a NEW ERA in anæsthetics and in surgery."

---

* COMRIE, J. D. (1932). History of Scottish Medicine. 2nd ed. London: Bailliere, Tindall and Cox, for Wellcome Hist. Med. Museum.

(5) & (6) That ether was soon used in general surgery and midwifery.

"(7) That on the 15th November, 1847, the anæsthetic effects of chloroform were discovered in Edinburgh. . . ."

Simpson undertook screening experiments, of a kind that would now only be done on animals, on himself and his colleagues. He tested a variety of substances. "Late one evening" in 1847 "on returning home after a weary day's labour, Dr. Simpson, with his two friends and assistants, Drs. Keith and Matthews Duncan, sat down to their somewhat hazardous work in Dr. Simpson's dining-room. Having inhaled several substances, but without much effect, it occurred to Dr. Simpson to try a ponderous material, which he had formerly set aside on a lumber-table, and which, on account of its great weight, he had hitherto regarded as of no likelihood whatever. That happened to be a small bottle of chloroform. It was searched for, and recovered from beneath a heap of waste paper. And, with each tumbler newly charged, the inhalers resumed their vocation. Immediately an unwonted hilarity seized the party; they became bright-eyed, very happy and very loquacious—expatiating on the delicious aroma of the new fluid. The conversation was of unusual intelligence, and quite charmed the listeners—some ladies of the family. . . ." There was a crash. "On awaking, Dr. Simpson's first perception was mental—'This is far stronger and better than ether' said he to himself. His second was to note that he was prostrate on the floor and that among the friends about him there was both confusion and alarm." Dr. Duncan was unconscious beneath a chair and Dr. Keith was struggling.

It is significant that the first two effective general anæsthetics, nitrous oxide and ether, are still, when used together, after more than 100 years, the safest choice for an unpractised doctor who finds himself obliged by circumstances to administer a prolonged anæsthetic.

The next important developments in anæsthesia were in the 20th century when the introduction of new drugs and new apparatus increased the range of anæsthesia and as a result, the range of the surgeon.

The Mode of Action of Anæsthetics

The mode of action of anæsthetic agents is unknown. There are no known properties which are common to every agent and so it is possible that there are several different modes of action.

Many are very fat-soluble and there is some correlation between this and anæsthetic potency; the more fat-soluble tend to be the more potent anæsthetics, but such a correlation cannot be applied generally. Some anæsthetic agents are not fat-soluble and many fat-soluble substances are not anæsthetic agents. It is likely that effects on cell membranes, colloids, cell oxidative processes and utilisation of energy derived from oxidation are concerned in producing anæsthesia and it is unlikely that, when explanations of anæsthetic action are eventually found, they will be simple.

Stages of Anæsthesia

Anæsthesia is conventionally divided into four stages, and the third stage again subdivided into four planes; obviously these all merge one with the next.

Stage 1. Analgesia

Analgesia is partial until stage 2 is about to be reached. Consciousness and sense of touch are retained and sense of hearing is increased.

Stage 2. Delirium

The patient is unconscious, but automatic movements may occur. He may shout coherently or incoherently, become violent or leap up and run about. The prevention of these unpleasant manifestations lies in a skilful, smooth and quick induction in quiet surroundings. Sudden death, probably due to vagal inhibition of the heart or to sensitisation of the heart to adrenaline by the anæsthetic agent, may occur in a violent second stage.

Stage 3. Surgical Anæsthesia

This is divided into four planes and the required depth differs according to the kind of operation to be performed. Depth is determined by noting characteristic changes in respiration, pupils, spontaneous eyeball movements, reflexes and muscle tone.

Stage 4. Medullary Paralysis

Arrival at this stage constitutes an anæsthetic accident.

General Points About Anæsthetics

The practice of the modern anæsthetist has three main components:—

1. Before surgery, the preparation of the patient for surgery by premedication as well as assessment of his physical condition, which may very well affect the choice of drugs in 2.

2. During surgery, the production of hypnosis, analgesia and muscular relaxation as required.

3. After surgery, the relief of pain and other aspects of postoperative care.

These three components are interdependent, the choice of drugs to be used at any one point affecting the choice of drugs both before and after, for instance drugs used in premedication may reduce both the amount of general anæsthetic and the postoperative medication required. Safety and comfort for the patient and good operating conditions for the surgeon are all desirable, but the provision of one may compromise the others. The problem may be approached in many different ways, using different combinations of the wide array of drugs which are available.

Simplicity leads to safety, for it is much easier to reach a clear diagnosis when few drugs have been given than when many drugs have, inevitably, confused the picture. Safety does not lie in numbers where drugs are concerned.

The techniques of administration of anæsthetic drugs and physical control of respiration are of great importance, but are outside the scope of this book.

Before Surgery, Premedication

The principal aims are to provide:—

Sedation and Amnesia. A patient who is going to have a surgical operation is naturally apprehensive and drugs may be used to reinforce reassurance. This is not solely humanitarian, for the discharge of adrenaline from the suprarenal medulla and the increased metabolic rate which are concomitants of anxiety render the patient both more difficult to anæsthetise and more liable to cardiac arrhythmias with some anæsthetics (cyclopropane, halothane, trichloroethylene, chloroform).

Every hypnotic, sedative and tranquillising drug has been applied to this purpose and claimed to have special utility, but morphine, morphine derivatives, hyoscine and barbiturates can fill most needs.

Analgesia, if there is existing pain or if it is desired to supplement a weak anæsthetic agent, such as nitrous oxide, to be used later. Analgesia is not required if there is no existing pain and a potent agent such as ether is to be used.

Inhibition of the Parasympathetic nerve supply to:

(i) the lungs to reduce respiratory tract secretions, which are liable to be profuse if an irritating drug such as ether is used, and to reduce any tendency to bronchospasm,

(ii) the heart (vagus) to reduce the likelihood of cardiac arrhythmias. Atropine or hyoscine are generally used.

Many drugs used in premedication are synergistic with the main anæsthetic agents. Failure to remember this may result in overdose, so that severe respiratory depression may occur, and delayed recovery which increases the risk of pulmonary complications. Chlorpromazine potentiates most anæsthetic agents, but particularly barbiturates. It also potentiates neuromuscular blocking agents, but this may not be clinically important.

Typical combinations used in premedication include:—

morphine		hyoscine
or		or
papaveretum	plus	atropine
or		or
pethidine		promethazine

They are usually administered s.c. one hour before the operation (for dosage, see under individual drugs). The combination of morphine and atropine has been in use for over 80 years. Morphine and its derivatives are dangerous in the presence of raised intracranial pressure, respiratory obstruction or severe emphysema. Atropine and hyoscine, although the latter is a central depressant, tend to counteract the respiratory depressant effect of morphine by an unknown mechanism so that a combination with either of these two is satisfactory. Papaveretum (Omnopon) is said to cause less vomiting, and pethidine to cause both less vomiting and less respiratory depression than morphine, but there is some doubt about this, for many observations on side-effects have not been made with genuinely equi-analgesic doses of the drugs.

Barbiturates, such as quinalbarbitone or pentobarbitone, can be used orally with or without morphine in adults or children. Barbiturates only relieve pain when given in very high doses, and are liable to induce mental confusion if used without an analgesic in patients who are in pain, and so promote postoperative restlessness. In the case of children the aim is often to anæsthetise them whilst sleeping under premedication.

A well-known combination of newer drugs for premedication and as an adjuvant during anæsthesia, is promethazine 50 mg. and pethidine 100 mg. both given i.v. The merits claimed for this combination are based on clinical impressions of those who have used it and no scientific evidence exists which proves its superiority. Chlorpromazine and pethidine can also be combined to provide sedation and analgesia.

It is worth remembering that many drugs used in anæsthetic premedication, for instance morphine and atropine, alter the pupil size and that this will affect the utility of the pupils as a gauge of anæsthetic depth. If there is any reason to fear glaucoma, hyoscine should be used instead of atropine, or better still, neither.

The term "basal narcosis" is used for a state of unconsciousness which is not deep enough to allow surgery. It is commonly induced by oral barbiturates or by drugs such as bromethol or thiopentone given into the rectum. By both these routes absorption is relatively slow and erratic compared with the inhalation of gases, and a dose that can be relied upon to provide surgical anæsthesia is liable to be an overdose, or to cause unnecessarily prolonged unconsciousness, so that "basal anæsthesia" is not attempted.

During Surgery

The modern trend is to induce sleep, analgesia and muscular relaxation with separate drugs. This triad can be produced with a single drug in large doses but the consequences of the resulting deep anæsthesia are unpleasant and may be dangerous.

Sometimes operations are carried out on patients who are conscious but in a state of analgesia.

A Typical Anæsthetic consists of:—

Administration of a hypnotic drug, *e.g.* thiopentone.

Production of analgesia and maintenance of hypnosis with nitrous oxide and thiopentone.

Provision of extra analgesia as required, if nitrous oxide is insufficient, by (*a*) an inhalation agent, *e.g.* ether, trichloroethylene, or (*b*) an, analgesic i.v., *e.g.* pethidine.

Provision of muscular relaxation by (*a*) a neuromuscular blocking agent i.v. or (*b*) deep anæsthesia with an inhalation agent, *e.g.* ether, or (*c*) nerve block with a local analgesic, *e.g.* lignocaine.

In addition, special techniques such as the production of hypotension or hypothermia may be required.

Antidotes to the injected anæsthetics and analgesics are described elsewhere. Antidotes to the inhalation anæsthetics are seldom required, as the drugs are rapidly excreted from the lungs and recovery quickly occurs when they are withdrawn at non-toxic levels. Antidotes are however required for neuromuscular blocking agents. In the absence of an antidote artificial respiration must be continued until spontaneous breathing is adequate. Neuromuscular blocking agents are of two kinds (p. 135) and as the antidote to one kind may prolong paralysis if used with the other, it is essential to distinguish between the groups. It is obviously better not to use both types of drug in the same patient if there is any possibility of them both acting at once, for if there is delayed recovery it is difficult to know what to do, and also there can be some mutual antagonism.

Nerve conduction may be blocked at several sites, by infiltration under the skin, by depositing the local analgesic solution along the course of the nerve or by injecting the drug into the cerebrospinal fluid as a spinal cord anæsthetic. Nerve and spinal block provides its own muscular relaxation as motor fibres are blocked as well as sensory nerve fibres, although with care differential block can be achieved. Areas of selective sensory, but not motor nerve block, are found at the edges of some regional nerve blocks. Even when motor nerve fibres are intact, muscular relaxation will occur if the patient's consciousness is blunted with a hypnotic drug.

After Surgery

Relief of pain after surgery presents many problems. Morphine and its derivatives are commonly used, but since they constipate, may cause vomiting, and depress cough and respiration, it will be appreciated that they have disadvantages in certain surgical situations, for instance after operations on the bowel and chest. Pethidine neither constipates nor suppresses spontaneous cough significantly although it can be useful, given i.v., to reduce cough from an endotracheal tube.

An account of analgesics is given elsewhere.

Inhalation Anæsthetics

The requirements of the "ideal" anæsthetic gas* are strict and it is hardly surprising that they have not yet been met.

The Patient wants a fast and pleasant induction with a non-irritant gas with no unpleasant smell. He wants to recover comfortably too.

The Surgeon's requirements are that the gas should be non-explosive, should not increase capillary bleeding and should induce complete muscular relaxation.

The Anæsthetist wants the gas to have a wide safety margin (so does the patient), to alter normal physiology as little as possible and to be potent enough to allow adequate concentrations of oxygen to be administered with it. It should be absorbed and excreted unchanged and rapidly so that accurate control of induction, depth of anæsthesia and recovery can be achieved.

The Manufacturer would be content if the gas could be made and purified easily and cheaply and if it was unaffected by conditions and duration of storage.

It is likely that the ideal anæsthetic agent would be a gas. It is, for example, difficult to envisage the ideal drug being metabolised in the liver or excreted by the kidneys and remaining unaffected by disease of those organs. Pulmonary absorption and excretion seem to offer the best prospects of accurate control, even in the presence of pulmonary disease, except perhaps severe emphysema. For the present it is usual to attempt to overcome the disadvantages of each agent by using a combination of drugs in such a way that the disadvantages of each are less prominent. Examples include the induction of anæsthesia with an i.v. injection of a barbiturate to avoid the slow induction characteristic of ether; and the combination of ether with i.v. analgesics or neuromuscular blocking agents to avoid having to take the patient too deep with the ether with consequent delayed recovery and greater bronchial irritation.

---

* SEEVERS, M. H., and WATERS, R. M. (1938). *Physiol. Rev.*, **18**, 447.

ANÆSTHETIC DRUGS

Ethyl Ether (1842)

Ether is relatively non-toxic and is justly reputed to be a safe drug even in relatively unskilled hands. This is because the blood level which stops respiration is much less than that which stops the heart, so that there is greater opportunity to retrieve the situation. It is easier to provide artificial respiration for a time than it is to restart an arrested heart.

"Unfortunately, with the advance of modern methods, ether has come to be regarded as 'old-fashioned', and an anæsthetist administering it as 'out-of-date'. As a result, too many anæsthetists have for too long tried to avoid its use for reasons entirely unconnected with the merits and demerits of the drug. . . . Experience has shown that, in the long run, the simplest methods are the best."*

However, ether is not free from disadvantages. The pungent smell is objectionable and induction of anæsthesia with ether alone is slow and therefore unpleasant for the patient. Irritation of the respiratory tract by the vapour leads to coughing, laryngeal spasm and increased mucus secretion. Ether also causes some vasodilatation which, in the third plane of the third stage may be great enough to cause severe fall in blood pressure. It also causes increased capillary bleeding.

A vigorous sympathetic autonomic response normally occurs during ether anæsthesia and counteracts the circulatory effects. If this response fails then circulatory collapse may occur. The hyperglycæmia that occurs with ether results from the release of adrenaline. Ether interferes with the homeostatic mechanisms in peripheral circulatory failure more than does cyclopropane.

If ether anæsthesia is deep and prolonged, recovery is liable to be slow and postoperative vomiting occurs, probably due to swallowing saliva containing ether. Beside these disadvantages must be placed the very practical advantage that anæsthetic deaths with simple techniques using ether are less common than with more complicated techniques employing other drugs.

Liquid ether boils at 35° C. (95° F.) and so may prove inconvenient in very hot climates. The vapour is explosive and as it is heavier than air a dangerous layer may accumulate near the floor of the operating theatre. Ether is absorbed and excreted almost entirely by the lungs.

---

* Gould, R. B. (1954). *In* Modern Practice in Anæsthesia. Ed. F. T. Evans. London: Butterworth.

When the open drop method of administration is used it is important to avoid getting ether into the eyes or on to the skin because it is irritant. The same applies to chloroform.

A very rare complication of ether anæsthesia is "ether convulsions". They are thought to be the result of a combination of circumstances and are most common in children. They are promoted by deep anæsthesia, sepsis, atropine premedication, fever or overheating, and carbon dioxide retention. They are dangerous and can be largely avoided. Treatment is by cooling and i.v. barbiturate for the convulsions; oxygen and artificial respiration by positive pressure may be needed after giving the barbiturate because convulsions are followed by respiratory depression, which is increased by the treatment.

Ether decomposes, forming toxic aldehydes and peroxides, unless protected from light and heat. Addition of carbon dioxide and copper delay decomposition. Very old ether should be suspected and discarded if possible.

Divinyl Ether (1930) is very potent indeed. It can provide quick induction and quick recovery. A natural corollary of this is that its action is difficult to control. It is used for rapid induction, after which the anæsthetic is carried on by other agents, but it can be used alone for brief operations. It is explosive, very volatile, boiling at 28° C. (83° F.), and chemically unstable. It can cause liver damage and excessive salivation is liable to be a nuisance when it is used.

Ethyl Chloride (1844)

Ethyl chloride boils at 12° C. (54° F.) and so has to be kept under pressure if it is to be liquid at room temperature; it is somewhat explosive. Ethyl chloride is extremely potent and therefore dangerous and is sometimes used for rapid induction of anæsthesia. It sensitises the heart to adrenaline. Because of its extreme volatility it may be used for local analgesia for which purpose it is sprayed on the skin, and in vaporising removes heat, thus cooling and paralysing sensory nerve endings. Prolonged inhalation, which should never occur, causes toxic effects similar to those of chloroform.

Nitrous Oxide (1844)

Nitrous oxide is an entirely safe anæsthetic gas *provided that it is used correctly*. Untoward effects are due to associated anoxia due to improper use. It is comparatively impotent and cannot alone maintain full surgical anæsthesia. For this reason it is commonly used in conjunction with analgesics or as a vehicle for other inhalants such as ether. It is used alone for very brief operations (*e.g.* dental). Induction and recovery are rapid.

Nitrous oxide, inhaled as a 45 to 50% mixture with air, may be used as a self-administered analgesic in obstetrics.

Nitrous oxide is not explosive but supports combustion.

Chloroform (1847)

Chloroform is now but little used in hospital practice as it is generally considered too dangerous, but like so many drugs generally labelled as dangerous its undesirable properties can be minimised by skill and familiarity, so that it can compare favourably with a "safer" drug handled badly. In domiciliary practice the safer inhalation substitutes for chloroform are at a disadvantage for they either require complicated apparatus or are less potent and more unpleasant. Chloroform is easy to administer, very potent and not extraordinarily unpleasant to inhale, so that for use in out-of-the-way places it is very convenient. It is absorbed and excreted through the lungs. It boils at 61° C. and is not explosive. These advantages are offset by its dangers, the principal being hepatic necrosis, the manifestations of which may be delayed for a few days after the operation. In addition, chloroform sensitises the heart to adrenaline so that if there is a violent second stage of anæsthesia the accompanying endogenous secretion of adrenaline may cause fatal ventricular fibrillation. Chloroform vapour is heavier than air, more so than ether, and when given by dropping on an open mask there should be no padding between the mask and face, as too high a concentration of vapour may occur in a mask thus sealed against the face.

Chloroform decomposes if exposed to light, air and alkalis, and any liquid remaining in an anæsthetic machine after a session should be discarded.

Cyclopropane (1929)

Cyclopropane is a very potent, relatively explosive, non-irritant gaseous anæsthetic absorbed and excreted through the lungs. Two advantages are that deep anæsthesia may be maintained with an adequate oxygen intake and that depth can be varied very rapidly. It sensitises the heart to adrenaline and this, together with the carbon dioxide retention which results from respiratory depression, tends to promote cardiac arrhythmias. Patients are prone to develop laryngospasm. When the cyclopropane is withdrawn there is sometimes a sudden drop in blood pressure, "cyclopropane shock", which is said to be due to the rapid fall in carbon dioxide in the blood. It is used in closed circuit chiefly because it is expensive.

Trichloroethylene (1934)

Trichloroethylene is similar to chloroform but less toxic. It is not used for deep anæsthesia because it is liable to cause tachypnœa and respiratory irregularity or arrest. It is used as a supplement to nitrous oxide in surgical operations, and, in special inhalers which prevent overdose, it can be used by self-administration in obstetrics and any severe recurrent pain.

Trichloroethylene should not be used in carbon dioxide absorption systems for it decomposes in contact with soda lime to form toxic products which may be the cause of cranial nerve damage (especially 5th nerve). It also decomposes if exposed to light and air. It is non-inflammable and non-irritant in anæsthetic concentrations.

Halothane (1956)

Halothane (Fluothane) is a liquid boiling at 50° C. It is potent and expensive, non-irritant and non-explosive. It causes hypotension, especially with curare, cardiac arrhythmias and tachypnœa. The place of halothane in anæsthesia remains to be decided.

Bromethol (1926)

Bromethol (Avertin) may be used for basal narcosis and also as an anticonvulsant in status epilepticus, eclampsia, or tetanus. It is toxic, like chloroform, if used in excess and so the dosage advised below should not be exceeded. It is detoxicated in the liver and excreted by the kidneys and so disease of these organs are relative contra-indications to its use. There is no specific antidote to overdosage. It is inflammable.

Bromethol is a solution of tribromoethyl alcohol in amylene hydrate. For basal narcosis 0·1 ml./Kg. up to a maximum total dose of 8 ml. for women and 10 ml. for men is dissolved in 30 to 40 ml. distilled water or saline at body temperature, and is infused rectally over four minutes about 45 minutes before surgery. The patient should be asleep in 10 minutes and, like all anæsthetised patients, should not be left unattended because of the risk of suffocation. Bromethol is very unstable and on decomposition forms hydrobromic acid which is intensely irritant. To determine whether it is safe to use a particular sample, congo red should always first be added. If it remains red it is safe, if it turns blue it must all be discarded. Solutions *must* be used at once and never kept. Attention to detail when using the drug is essential.

Paraldehyde (p. 102) **for Basal Narcosis.** 0·5 ml./Kg. but never more than 25 ml., diluted to a 10% solution, is given by rectum.

Thiopentone (p. 132) **for Basal Narcosis.** 45 mg./Kg. as a 5% solution, with maximum of 3 G., is given by rectum. A 10% solution is often used but is irritant.

Intravenous Anæsthetics

Thiopentone Sodium is the most widely used intravenous anæsthetic. It is injected as a 2·5 or 5% solution, the latter being prone to cause venous thrombosis. Thiopentone is very potent and quick acting and is especially suited to providing a pleasant induction. Anæsthesia may be induced by injecting 2 to 3 ml. of 2·5% solution in 20 to 30 seconds and then waiting a minute, and repeating this until the desired depth is reached. Laryngospasm is comparatively frequent. The great rapidity with which a patient may pass through the stages of anæsthesia means that the first obvious sign of overdose may be apnœa. Great care is therefore necessary when using thiopentone. Anæsthesia may be continued by adding analgesics such as i.v. pethidine, or inhalants such as nitrous oxide or ether. It is not an analgesic and is therefore unsatisfactory by itself for very painful operations, struggling and laryngospasm resulting from any attempt to use it thus. Other disadvantages are respiratory depression which is relatively greater for a given degree of muscular relaxation than is the case with inhalation agents, and regurgitation of gastric contents which may be silent and so unnoticed. It is dangerous in shocked patients.

Thiopentone is metabolised slowly by the liver and other body tissues. The comparatively rapid recovery from a single dose is due to diversion of the drug into the body fat in which it is soluble and from which it is later released and metabolised. This explains how it is that rapid recovery may follow several repeated doses of thiopentone until the time comes when the fat can store no more drug. A further dose then produces prolonged anæsthesia, as recovery now depends on destruction of the drug and not diversion into storage. It is inadvisable to exceed a total of 1·5 G. thiopentone in any operation.

Injection other than into the vein is very dangerous. If it is given subcutaneously the skin may slough. Given into or around a nerve (usually the median), permanent palsy may follow. To dilute the irritant solution, and to induce local hyperæmia to hasten absorption, 0·5% procaine may be injected into the site. In the case of nerve injury it may be desirable to incise the area and try to wash out the drug. If thiopentone is accidentally injected into an artery, thrombosis occurs and amputation may even become necessary. Treatment of this mishap is to heparinise the patient immediately and perhaps to sympathectomise the limb. There is evidence that the use of vasodilator drugs is not helpful.* The arm should be kept cold to reduce oxygen requirements. Surgical removal of the clot may be tried after about six hours if there is no improvement in the physical signs. Heparin may be continued, or oral anticoagulant therapy instituted, with allowance for surgery, until it is sure that all is well, which will probably mean about a week. Serious consequences from these mishaps are unlikely if 2·5% solution rather than 5% solution is used, and damage to arteries or nerves is less likely if the lateral border of the forearm and the back of the hand are chosen for injection and the vessel is palpated (without a tourniquet on the arm) before inserting the needle.

---

* Kinmonth, J. B., and Shepherd, R. C. (1959). *Brit. med. J.*, ii, 914.

There are numerous other barbiturates which can be used instead of thiopentone. None have proved superior.

Other intravenous anæsthetics are:—

Hexobarbitone Sodium. This is very similar to thiopentone with the same pattern of storage and metabolism. Recovery is less predictable, but it is less irritant.

Thialbarbitone, Thiamylal, Buthalitone. The sodium salts of these barbiturates may all be used for intravenous anæsthesia. They are not superior to thiopentone.

Steroid substances, such as hydroxydione, have been found to be anæsthetics. Their place is not settled.

NEUROMUSCULAR BLOCKING AGENTS

These substances first attracted scientific notice because of their use as arrow poisons by the natives of South America, who use the most famous of all, curare. Specimens of crude curare had been reaching Europe before 1811 when Sir Benjamin Brodie smeared "woorara paste" on wounds of guinea-pigs and noted that death could be delayed by inflating the lungs through a tube introduced into the trachea. He did not attempt to avoid death altogether, but did suggest that the drug might be of use in tetanus. A year later the traveller Charles Waterton visited South America to seek "the deadly wourali poison".* He obtained a specimen and tried it on a sloth, "from the time the poison began to operate, you would have conjectured that sleep was overpowering it and you would have exclaimed, 'Pressitque jacentem, dulcis et alta quies, placidæque simillima morti'." He also used it on an ox "whose flesh was very sweet and savoury at dinner". Having noted that "it totally destroys all tension in the muscles" Waterton turned to experiment with reputed antidotes on a fowl. He held the bird up to its mouth in water, poured sugar cane juice and rum down its throat and filled its mouth with salt; the bird died. He discussed the most promising antidote but did not then try it: "It is supposed by some, that wind introduced into the lungs by means of a small pair of bellows, would revive the poisoned patient, provided the operation be continued for a sufficient length of time. It may be so; but this is a difficult and a tedious mode of cure."

---

* WATERTON, C. Wanderings in South America. Revised edition 1828. Reprinted by Hutchinson, London, 1906.

On his return to England he experimented on a donkey which "died apparently" in ten minutes. He incised the windpipe and inflated the lungs with bellows for two hours which "saved the ass from final dissolution". She recovered, was named Wouralia, and was kept in luxury for a further 25 years as reparation.

Despite attempts to use curare for a variety of diseases including epilepsy, chorea and rabies, the lack of pure and accurately standardised preparations as well as the absence of convenient routine techniques of artificial respiration if overdose occurred, prevented it from gaining any firm place in medical practice until 1942, when these difficulties were removed.

Muscular Relaxation is often required to ease the surgeon's task. It may be achieved by:—

Deep general anæsthesia.
Nerve block with local anæsthetics.
Drugs acting on the central nervous system (mephenesin, meprobamate, chlorpromazine).
Drugs acting at the myoneural junction (tubocurarine, gallamine, decamethonium, suxamethonium).

Drugs in the last two groups are usually described as "*muscle relaxants*". Relaxation is more easily controllable and post-anæsthetic complications are less if light anæsthesia is used with neuromuscular block instead of deep general anæsthesia.

Relaxation by centrally acting drugs is incomplete and unsatisfactory, does not abolish respiration nor prevent voluntary movements nor withdrawal from painful stimuli. These drugs are not used in anæsthesia for this purpose, but chlorpromazine is used for other reasons. The centrally acting relaxants are described under tranquillisers (p. 206).

Drugs acting at the myoneural junction produce complete paralysis of all voluntary muscle so that movement is impossible and artificial respiration is needed. Attempts to achieve selective relaxation, sparing respiration, with these drugs, have met with little success as the dose level is critical in the few patients in whom this can be achieved.

The necessity for artificial respiration no longer deters anæsthetists who are now quite accustomed to taking over respiration from the patient as a routine. It is less easy to decide whether a patient is unconscious if he is paralysed (7).

Neuromuscular Transmission and its Modification by Drugs

When an impulse passes down a motor nerve to voluntary muscle it causes a release of acetylcholine at the nerve endings. This modifies the condition of the membrane of the motor end-plate, a specialised area on the muscle fibre. In its resting state the inside of the membrane has a negative and the outside a positive electrical charge. The acetylcholine causes a change in the permeability of this membrane to ions so that it is as though two solutions of different composition on the two sides were suddenly brought together. This results in a small and brief electrical potential, the end-plate potential, which fires off the action potential which is associated with contraction of the muscle.

In its resting state, with negative and positive potentials separated by a relatively impermeable membrane, the end-plate is said to be polarised, and the action of acetylcholine causing a sudden increase of permeability is said to depolarise it.

Neuromuscular blocking agents used in clinical practice interfere with the process described above. They do not affect either muscle or nerve, nor do they interfere with acetylcholine release.

However, substances which prevent the release of acetylcholine at nerve endings exist. Procaine in large doses does this and so does botulinum toxin.

There are two principal mechanisms by which drugs used clinically interfere with neuromuscular transmission:

By Competition (Tubocurarine, Gallamine)

It seems that these drugs can combine with, and block, the drug receptors on the motor end-plate which are the normal site of action of acetylcholine. Tubocurarine and gallamine "compete" with acetylcholine for these receptors. They do not cause depolarisation themselves but they protect the end-plate from depolarisation by acetylcholine. The result is a flaccid paralysis.

Reversal of this type of neuromuscular block can be achieved with anticholinesterase drugs, such as neostigmine, which prevent the destruction of acetylcholine released at nerve endings and so allow the concentration to build up, thus reducing the competitive effect of a given concentration of blocking agent.

By Depolarisation (Decamethonium, Suxamethonium)

These drugs imitate the action of acetylcholine at the motor end-plate and at their first application voluntary muscle contracts. It might be expected that this prolonged depolarisation would result in muscles remaining contracted, but this is not so (except in chickens), probably because the drug also causes a decrease in excitability of the end-plate and the area around it; thus, although a standing depolarisation of the end-plate exists, it is not strong enough to send the muscle into contraction. The cause of neuromuscular block by these drugs may therefore be the reduction in excitability of the muscle rather than the depolarisation,* although these two effects may be interdependent.

Anticholinesterase drugs in huge doses can produce neuromuscular block by depolarisation, but cannot be used clinically for this purpose because of their effect on the central and autonomic nervous systems. Anticholinesterases are thus not only useless as antidotes to depolarising drugs but may even increase the paralysis. However, it has been demonstrated in animals that after repeated doses, decamethonium or suxamethonium lose their depolarising effect and produce a competitive neuromuscular block similar to that of curare, and this is reversible by anticholinesterases. The reason for this is obscure. If this dual type of block, first depolarising, then competitive, occurs in man it could account for some cases of delayed recovery and the fact that neostigmine has sometimes been used as an antidote with success.

Neuromuscular Blocking Agents Acting by Competition

Tubocurarine† is an alkaloid which produces neuromuscular block by competition with acetylcholine. The peripheral site of action of curare was demonstrated by Claude Bernard in 1850 in a famous series of simple experiments on frogs. Its chief use is to provide muscular relaxation during surgery without the disadvantages of deep anæsthesia. Its introduction into surgery made it desirable to decide once for all whether the drug itself altered consciousness. Until 1947 there were doubts on this point. They were resolved in a single experiment.‡ A normal subject was slowly curarised after arranging a detailed and complicated system of communication. Twelve minutes after beginning the slow infusion of curare, the subject, having artificial respiration, could move only his head. He indicated that the experience was not unpleasant, that he was mentally clear and did not want an endotracheal tube inserted. After 22 minutes, communication was possible only by slight movement of the left eyebrow and after 35 minutes paralysis was complete and direct communication lost. An airway was inserted and the subject's eyelids were lifted for him with resulting appropriate inhibition of alpha rhythm of the electroencephalogram, suggesting that vision and consciousness were normal. After recovery, aided by neostigmine, the subject coported that he had been mentally "clear as a bell" throughout, and confirmed this by recalling what he had heard and seen. Interestingly, the insertion of the endotracheal airway caused only minor discomfort, perhaps because of the prevention of reflex muscle spasm. During artificial respiration he had "felt that (he) would give anything to be able to take one deep breath" despite adequate oxygenation.

---

* Paton, W. D. M. (1958). *In* Modern Trends in Anæsthesia. Ed. F. T. Evans and T. C. Gray. London: Butterworth.

† Curare is the crude plant preparation. The word is often used loosely when one of the pure alkaloids is, in fact, intended.

‡ Smith, S. M., *et al.* (1947). *Anesthesiology*, **8**, 1.

It is therefore essential to ensure that curarised patients do not regain consciousness unnoticed during surgery (7). That this is not merely a theoretical risk is shown by the occasion when an anæsthetist was horrified to be addressed thus by a patient who had had a pancreatectomy: "As a matter of fact, doctor, I woke up in the theatre." She remembered going to sleep and being woken "by the most excruciating pain in my tummy. It felt as if my whole inside were being pulled out": she wanted to attract attention "but I couldn't move any part of me. I heard the doctors talking about the gall-bladder and about doing something with it to the small intestine. . . ."*

In addition to its neuromuscular blocking effect tubocurarine blocks autonomic ganglia and causes histamine to be released. Both these effects may cause a transient drop in blood pressure and the latter may induce bronchospasm.

Curare is insignificantly absorbed from the alimentary tract, a fact known to the South American Indians who use it to procure food, as well as in war.

After an intravenous injection the action is maximal in four minutes and lasts about 30 minutes.

Tubocurarine is partly excreted unchanged in the urine and partly metabolised. Renal disease does not seem to be a contra-indication to its use, probably because the brief action of single doses is due to redistribution of the drug in the body and not to its disposal. It follows therefore that repeated use over a few days may result in prolongation of action of the later doses.

Tubocurarine is well tolerated at all ages, except perhaps in neonates.

Tolerance does not occur. Ether, which has a slight curare-like action, potentiates tubocurarine and so does chlorpromazine. There is considerable individual variation in response and some anæsthetists advocate the use of a small test dose.

Apart from occasional prolongation of action for unknown reasons, after-effects of tubocurarine are slight, although diplopia may rarely continue for a few days.

The action of tubocurarine may be antagonised by anticholinesterase drugs. Neostigmine (1·0 to 2·5 mg. of the methylsulphate) is usually given intravenously preceded if possible by atropine sulphate (1 mg.) to prevent the parasympathetic autonomic effects of the neostigmine. If the pulse rate slows unduly after the neostigmine more atropine may be given. The patient may relapse into paralysis again and so must be carefully watched. Too much neostigmine can cause neuromuscular block by depolarisation and can thus present a very confusing picture unless there have been some signs of recovery before neostigmine is administered.

---

* WINTERBOTTOM, E. H. (1950). *Brit. med. J.*, (*i*), 247.

It is theoretically undesirable to give atropine and neostigmine in full doses intravenously simultaneously, for atropine, before blocking the vagus nerve, causes, by a central action, transient vagal stimulation. If this is added to the effect of neostigmine, undue cardiac slowing may result. It is probably safer if atropine is given a few minutes before the neostigmine.

It is best to avoid the use of neostigmine whenever possible by allowing the effect of the tubocurarine to wear off whilst the patient is still supervised by the anæsthetist.

Tubocurarine is given as either the chloride (15 to 20 mg. i.v.), or as dimethyl tubocurarine bromide (2 to 4 mg. i.v.). Both drugs may be injected i.m.

Whenever tubocurarine is used artificial respiration will probably be needed. It is provided by inflating the lungs with appropriate gases (intermittent positive-pressure respiration, I.P.P.R.). Although muscular paralysis is selective, respiratory muscles being nearly the last to be affected, in practice it has not been possible to use tubocurarine effectively and safely in the treatment of convulsions and disorders of muscle tone without interfering with respiration.

Gallamine and Laudexium are synthetic drugs which act in the same way as tubocurarine, the former for a slightly shorter and the latter for a slightly longer time. They do not release histamine. Gallamine is excreted unchanged in the urine; it causes tachycardia. 80 mg. of gallamine triethiodide or 30 mg. of laudexium methylsulphate are equivalent to 15 mg. of tubocurarine chloride.

Neuromuscular Blocking Agents Acting by Depolarisation

Decamethonium blocks neuromuscular transmission by depolarisation. Paralysis is rarely preceded by muscular fasciculation. It is excreted in the urine. It acts for about 20 minutes, a shorter time than tubocurarine. No clinically useful antidote is available. Pentamethonium has some antagonistic effect but its ganglion-blocking actions render it unsuitable for clinical use. Neostigmine usually makes paralysis due to decamethonium worse. The dose of decamethonium iodide is 2 to 5 mg., i.v. or i.m.

Suxamethonium (succinylcholine) blocks neuromuscular transmission by depolarisation. Paralysis is usually preceded by muscular fasciculation. It acts for less than five minutes and is particularly useful for brief procedures such as tracheal intubation or electric convulsion therapy. Suxamethonium is destroyed by plasma cholinesterase and so its persistence in the body is increased by neostigmine which inactivates that enzyme, and in patients with hepatic disease or severe malnutrition whose plasma enzyme levels may be lower than normal. Procaine also is destroyed by plasma cholinesterase and so, by competing with suxamethonium for the enzyme, may prolong its action and vice versa. In addition there are individuals congenitally without this enzyme who cannot destroy the drug. The i.v. dose is 10 to 50 mg. of the chloride. Continuous i.v. infusions (2 to 3 mg./minute) or intermittent doses can be used for more prolonged and readily variable relaxation. Post-operative muscle pain is a prominent feature with suxamethonium.

Uses of Neuromuscular Blocking Agents

All neuromuscular blocking agents, except suxamethonium and laudexium may be mixed in a syringe with thiopentone.*

Drugs acting by competition may antagonise those acting by depolarisation and it would seem better not to use them simultaneously. A dose of suxamethonium for tracheal intubation followed by curare some minutes later, after its action has worn off, would not, of course, be objectionable.

The effect of temperature on the response to neuromuscular blocking drugs may have practical importance. Patients may be cooled deliberately when "hypothermia" is used, or accidentally, *e.g.*, if large areas of intestine are exposed in a cool operating theatre. Curare-like drugs are rendered less effective and depolarising drugs more effective by lower temperatures. When a curarised patient is warmed up after an operation the curare remaining in the body becomes more effective and may re-paralyse the patient (*9*).

Neuromuscular blocking agents should only be employed by those who have received special training in their use.

In Surgery they are used to provide muscular relaxation.

In Convulsions (*e.g.* electric convulsion therapy) they are used to prevent injury due to the violence of the fit. In status epilepticus or convulsant drug poisoning, neuromuscular blocking agents with artificial respiration are not the drugs of choice although they can be used. In tetanus their use has not yet been shown to reduce mortality.

In Diagnosis of Myasthenia Gravis the characteristically increased sensitivity to curare and the decreased sensitivity to decamethonium have been used as indicators. It is a dangerous technique only to be employed in otherwise undiagnosable cases with apparatus for artificial respiration at hand.

---

* Some preparations of tubocurarine cannot be mixed.

LOCAL ANALGESICS*

Cocaine was the first local analgesic discovered. It was isolated in 1860 and suggested as a local analgesic for clinical use in 1879. Nothing however was done until 1884 when Dr. Sigmund Freud in Vienna was reinvestigating the alkaloid, and invited Dr. Carl Koller to join him. The latter had long been interested in the problem of local analgesia in the eye, for general anæsthesia has disadvantages in ophthalmology. On observing the numbness of the mouth caused by taking cocaine orally he realised that this was a local anæsthetic effect. He tried cocaine on animals' eyes and introduced it into clinical ophthalmological practice†, whilst Freud was on holiday. Freud had already thought of this use and discussed it, but had gone off to see his fiancée. The use of cocaine spread rapidly and it was soon being used to block nerve trunks. Chemists then began to search for less toxic substitutes with the result that procaine was introduced in 1905.

Innumerable compounds have local analgesic properties, but comparatively few are suitable for clinical use. Suitable substances must be water-soluble, non-irritant, have a rapid onset of effect, a duration of action suitable for the operation to be performed, be non-toxic when absorbed into the circulation, and leave no local after-effects.

The way in which local analgesics act is unknown, but they probably produce their effects on nerves at the nodes of Ranvier where the myelin sheath does not extend and where ion exchanges are known to take place. However, they affect cell bodies as well as nerves and act on all nervous tissue to prevent impulses from arising or passing. They paralyse afferent nerve endings, sensory and motor nerve trunks and the central nervous system, although they may stimulate the latter first.

The fibres in nerve trunks are affected in order of size, the smallest (sensory) first, probably because they have a proportionately high surface area, and then the larger (motor) fibres.

Most local analgesics are used in the form of the acid salts, as these are stable compounds. The acid salt must dissociate in the tissue to liberate the free base before the analgesic effect can occur. This dissociation is delayed in abnormally acid, *e.g.* inflamed, tissues. The risk of spreading infection also makes local analgesia undesirable in infected areas.

---

* The term "local analgesic" has largely replaced "local anæsthetic" in British terminology. The drugs can, however, abolish all sensation and not merely pain. In the usual doses touch may be spared.

† Koller, C. (1928). *J. Amer. med. Ass.* **90**, 1742.

Local analgesics are usually effective within five minutes of application and last one to two hours. Their action may be prolonged by adding adrenaline or noradrenaline, about 1 part in 100,000, to the analgesic solution, to reduce absorption by causing local vasoconstriction. This also reduces systemic toxicity as less analgesic is needed to produce the local effect. If large amounts are used systemic effects may be produced by the adrenaline. The principal difference between adrenaline and noradrenaline that might be expected to be relevant to this use is the usual action of adrenaline as a vasodilator to muscle vessels, but in the relatively high concentration used adrenaline in fact causes vasoconstriction in the muscle. It also causes palpitations and anxiety and nervousness if too much is absorbed and noradrenaline might well be preferred. Vasoconstrictors should not be used with local analgesics where the whole vascular supply to a part might be affected, as in nerve block of fingers and toes. To promote the diffusion of local analgesics, hyaluronidase may be added to the injected solution, but this increases the absorption rate; it can be used with noradrenaline or adrenaline.

Procaine and amethocaine, which are derivatives of p-aminobenzoic acid, inhibit sulphonamide antibacterial activity. This probably has no significant effect in antagonizing sulphonamides throughout the body, but with wounds, or when local analgesia is being used for lumbar puncture or other exploration in sulphonamide-treated patients, local sulphonamide antagonism followed by infection may occur. Lignocaine does not antagonise sulphonamides.

Local analgesics also have the following effects in varying degree:—

1. Stimulation of the central nervous system which may show itself by anxiety, restlessness, tremors and even convulsions. These latter are very dangerous and are followed by respiratory depression. Barbiturates may be necessary to control the convulsions but may aggravate respiratory failure so that artificial respiration is needed. Respiratory stimulants are useless and dangerous as the patient has already passed through a phase of overstimulation.

2. Quinidine-like actions on the heart.

3. Relaxation of smooth muscle. This effect has been used in the treatment of asthma, but it is not a very valuable one.

4. Depression of neuromuscular conduction, but not to an extent which is clinically important.

Absorption of Local Analgesics from mucous membranes varies according to the compound. Those which are well absorbed are used as surface analgesics (cocaine, lignocaine, amethocaine, cinchocaine). Procaine is not significantly absorbed and is useless for this purpose. Absorption of topically applied local analgesics may be extremely rapid and give blood levels comparable to those obtained by injection. This has led to deaths from overdosage, especially via the urethra.

Fate of Local Analgesics. Most of these drugs are destroyed by enzymes in the blood and liver.

Uses of Local Analgesics. Local analgesia is generally used for trivial operations, when loss of consciousness is neither necessary nor desirable and also as an adjunct to major surgery to avoid deep general anæsthesia. It is seldom used alone for major surgery, not because it is impracticable but because the patients prefer unconsciousness. It is, however, invaluable when the surgeon is his own anæsthetist. Local analgesics can also be used topically for short periods to give relief from local pain or itching.

For any but the most trivial operation premedication with barbiturates is theoretically desirable both to counteract the central stimulant action of local anæsthetics and, in the case of cocaine, to counteract its potentiation of the effect of adrenaline on the central nervous system; but the doses used may in fact provide little or no protection.

Local analgesics may be used in a number of ways:—

1. Surface analgesia as solutions, ointments, or lozenges. Chronic use is liable to cause sensitisation.

2. Infiltration analgesia in which it is aimed to block the nerve endings and small cutaneous nerves in a given area.

3. Nerve block, to anæsthetise a region which may be small or large by injecting the drug around, not into, the appropriate nerves, usually either a peripheral nerve or a plexus. There are various specialised forms: paravertebral, epidural and caudal block. Sympathetic nerve blocks may be used in vascular disease to induce vasodilatation.

4. Spinal block, in which the drug is introduced into the subarachnoid space. By using a solution of appropriate specific gravity and adjusting the patient's posture the drug can be kept at an appropriate level. It can cause hypotension by blocking the sympathetic nervous system outflow if the block is at the right anatomical level. Serious local neurological complications have occurred both from the drug and from accidentally introduced bacteria. It is no longer popular for these reasons but may be useful in single-handed emergency.

The term "regional analgesia" is used for 3 and 4, and with both these techniques considerable knowledge of anatomy and attention to detail are essential for success with safety.

Toxicity of Local Analgesics. Excessive absorption results in nervousness, tremors and convulsions and these can be treated by barbiturates, given i.v. if necessary. Nausea, vomiting and abdominal pain may occur, and also sudden cardiovascular collapse and respiratory failure for which there is no specific treatment other than artificial respiration and cardiac massage as necessary. When systemic toxicity follows injection of a local analgesic into an extremity a tourniquet may be used to delay entry of what remains into the general circulation.

Hypersensitivity reactions such as rashes, asthma and anaphylactic shock, occur, and the subject may be sensitive to more than one local analgesic. Regular users of local analgesics are wise if they take care to keep them off their own skin when filling syringes.

APPROXIMATE DATA ON SOME WIDELY USED LOCAL ANALGESICS

TYPE OF ANALGESIA	*Procaine*	*Cocaine*	*Amethocaine*	*Cinchocaine*	*Lignocaine*
1. SURFACE					
Soln. strength	No effect	4%	2%	1%	2%
Effective in	—	5 mins.	5 mins.	10 mins.	5 mins.
Duration	—	30 mins.	40 mins.	—	1–2 hrs.
2. INFILTRATION					
Soln. strength ..	0·5%	Not used, too dangerous	0·1%	0·05%	0·5%
*Max. volume ..	300 ml.		100 ml.	200 ml.	125 ml.
3. NERVE BLOCK					
Soln. strength ..	1%	Not used, too dangerous	0·1%	Not used, may irritate nerve	1%
*Max. volume ..	125 ml.		50 ml.		50 ml.
Onset of effect 2 and 3	5 mins.	—	10 mins.	10 mins.	5 mins.
*Duration	1–2 hrs.	—	2–3 hrs.	3½–4 hrs.	2–4 hrs.
*Max. dose for an adult (injected)	1·5 G.	—	0·1 G.	0·1 G.	0·5 G.

* With adrenaline or noradrenaline; if these are not used to delay absorption, the total dose should be substantially less than above. If weaker solutions are used, larger volumes may be injected. Lozenges, lollipops for children, creams, ointments, jellies and suppositories are available for appropriate local use. As anæsthesia develops there is a danger of aspirating a lozenge into the trachea; captive preparations such as the lollipop are safer. All dosage figures apply to the hydrochlorides and are only approximate, larger amounts can often be given safely, but deaths have occurred with smaller amounts, so the minimum amount that will do the job should be used. Widely different solution strengths are used in some cases.

Routine tests for hypersensitivity have been advocated in all cases before injecting local analgesics. Their value is doubtful and they are very time consuming. A ship's cook aged 62 was to have a bronchogram performed because of suspected bronchial carcinoma. "He was given an amethocaine lozenge to suck, to indicate whether or not he was allergic to amethocaine. As he showed no reaction, half an hour later his throat was sprayed with 0·5 to 1 ml. of amethocaine solution. During this procedure he suddenly collapsed, had a convulsive fit, and died within three minutes."*

Local inflammatory or necrotic effects may occur, for these drugs can damage all cells. Procaine is less harmful in this respect than most.

LOCAL ANALGESIC AGENTS

Some approximate data on the most widely used local analgesics are given in the table on p. 143. See also p. 141.

Cocaine

Cocaine hydrochloride is used solely as a surface analgesic, usually as a 4% solution, because toxic effects are both common and dangerous when it is injected. Even as a surface analgesic sufficient absorption may take place to cause serious toxicity. Ear, nose and throat surgeons sometimes apply a little pure solid or 20% solution to small areas and do not consider it unduly dangerous used thus.

Cocaine potentiates adrenaline, perhaps by inhibiting the enzyme which destroys adrenaline in the body. General sympathomimetic effects occur. This is the cause of the dilatation of the pupil seen when cocaine is used on the eye and perhaps partly of the anxiety and tremors which are more prominent with cocaine than with other local analgesics.

Cocaine causes pyrexia in man by an action on the central nervous system which is assisted by the peripheral vasoconstriction resulting from its sympathomimetic action.

By mouth the only use for cocaine is in the relief of nausea and vomiting in patients dying of gastric carcinoma (initial dose 10 to 15 mg. cocaine hydrochloride).

Cocaine Addiction is widespread amongst South American natives who chew the leaves with lime to release the alkaloid. It is claimed to give relief from fatigue and hunger and to induce a pleasant introverted mental state. Remarkable feats of endurance attributed to chewing cocaine leaves have been reported, but there is no adequate scientific explanation of them. A United Nations enquiry into coca-leaf chewing reported that true physical dependence did not occur (*i.e.* there is no characteristic withdrawal syndrome) and it may be that the practice is more a habit than an addiction. It also reported that the habit caused physical exhaustion rather that the reverse, and advocated its gradual suppression in the interest of the populations concerned.[*]

---

* *Brit. med. J.* (1955), (*i*), 610.

In more "civilised" societies pure cocaine is used intermittently by its devotees to obtain pleasant interludes, and courage, sometimes for the commission of crimes. Continuous use leads rapidly to an acute toxic psychosis. Tolerance does not occur. The drug is taken as a snuff, "snow", by "snowbirds", who often develop nasal ulceration probably as a result of the accompanying vasoconstriction. It is also taken by self-injection, often intravenous.

Procaine

Procaine hydrochloride is not absorbed through mucous membranes and is useless as a surface analgesic. Details of dosage are given on p. 143. It is rapidly hydrolysed in the blood, which is an advantage when toxic doses have been given. Procaine and lignocaine are the most widely used local analgesics for injection. Procaine relaxes smooth muscle and has been used i.v. in resistant cases of asthma, and also as a general analgesic, although there is probably little justification for the latter use. Care is especially necessary to avoid overdose when it is given i.v.; by this route a maximum dose of 4 mg./Kg. may be given over 20 minutes as a 0·1% solution. Employment of its quinidine-like action against cardiac arrhythmias is no longer necessary now that procainamide is available.

Amethocaine and Cinchocaine

Amethocaine resembles cocaine more than procaine. It is used as the hydrochloride (p. 143) and is effective on surfaces as well as by injection. It is dangerous, being absorbed through mucous membranes with very great speed so that systemic toxic effects may occur.[†]

Cinchocaine resembles amethocaine. It is used as the hydrochloride (p. 143).

Lignocaine

Lignocaine is a successful drug which could be claimed to be the best for surface use as well as for injection, combining efficacy with comparative lack of toxicity. It is used as the hydrochloride, dosage details are given on p. 143. A rather surprising use for it has been found in cases of status epilepticus,[‡] when the more usual anticonvulsants have failed

[*] Report of commission of enquiry on coca leaf (April 1950). United Nations document E/1666.

[†] Campbell, D., and Adriani, J. (1958). *J. Amer. med. Ass.*, **168**, 873.

[‡] Taverner, D., and Bain, W. A. (1958). *Lancet*, (*ii*), 1145.

(up to 5 mg. Kg. by a slow, single i.v. injection, or up to 100 mg. minute by i.v. infusion). Other local analgesics may have this action. Overdose of lignocaine, however, can cause convulsions. Chemically, lignocaine differs from most other local analgesics and so is especially suitable for trial in cases of known hypersensitivity to other drugs.

There are numerous other local analgesics (*e.g.* amylocaine, benzocaine, butacaine, orthocaine), and their omission here is not meant to imply that good results are not obtainable with them.

Choice of Local Analgesic. The many agents available are proof that all have disadvantages and that no agent is unchallengeably the best for all occasions. This is particularly the case for surface analgesia, although a claim that lignocaine is safest and best could not easily be dismissed. For injection by the occasional user lignocaine or procaine are satisfactory. Professional anæsthetists will often choose from a wider range. There have been many deaths due to wrong concentrations of unfamiliar drugs being used, and to people being confused by the names which all end in "caine".

Obstetric Analgesia

Although this soon ceased to be considered immoral, it has been a technically controversial topic since 1853 when Queen Victoria, having inhaled chloroform during the birth of her eighth child, "expressed herself as grateful for the discovery of this means of alleviating and preventing pain." ". . . the acknowledged skill of the physicians who sanctioned the inhalation of the chloroform" was contested by the *Lancet* which recorded "intense astonishment . . . throughout the profession" at this use of chloroform, "an agent which has unquestionably caused instantaneous death in a considerable number of cases. . . . Probably some officious meddlers about the Court. . . ."*

Pain-free labour sometimes occurs spontaneously but, rightly or wrongly, most women in Western civilisations anticipate pain and prefer to use drugs. The reason for lack of general agreement on which drugs are best is that requirements are stringent, and much depends on the skill with which they are used. The ideal drug must relieve pain without making the patient confused or uncooperative. It must not interfere with uterine activity nor must it influence the fœtus (respiratory depression is the chief disadvantage and this may be due to direct action of the drug in the fœtus, to its prolonging labour and so causing fœtal anoxia, or to its reducing uterine blood supply). It should also be suitable for use by a midwife without supervision.

Innumerable schemes have been proposed and good results can be obtained with many, by those who take the trouble to familiarise themselves with them. Generally, strong analgesic drugs should not be started before uterine contractions are well advanced as they are liable to stop feeble contractions.

---

* Editorial (1953). *Brit. med. J.* (*i*), 824.

The following may be taken as a general guide:—

Early first stage of labour—mild sedatives (chloral, barbiturates) and mild analgesics (codeine).
End of first stage of labour—stronger analgesics (pethidine) and then trichloroethylene, or nitrous oxide and air.
Second stage of labour—trichloroethylene or nitrous oxide and air.

Pethidine is widely used. It seldom causes serious respiratory depression but has been shown to reduce respiratory minute volume in the baby.* Combination of 1·25 mg. of levallorphan per 100 mg. pethidine (Pethilorfan) to the mother may prevent this without noticeably diminishing analgesia. Morphine may depress fœtal respiration more than pethidine, and nalorphine administered to the mother before birth or to the child after birth will reverse the effect (p. 167).

Barbiturates combined with pethidine may produce severe fœtal respiratory depression.

The intervals between doses naturally vary greatly in a condition as variable as labour.

Nitrous oxide (85 to 90%) and oxygen (10 to 15%) may be administered for each pain or nitrous oxide (50%) and air (50%) can be used in a machine which the patient works herself.

Trichloroethylene in a special inhaler for self-administration is excellent.

Other drugs, opiates, methylpentynol and tranquillisers are being tried.

Obstetric Anæsthesia presents a special problem in that the safety of the fœtus must also be considered. All anæsthetics and analgesics in general use cross the placenta in varying amounts and, apart from respiratory depression, produce no important effects except that deep general anæsthesia interferes with uterine retraction and may be followed by uterine hæmorrhage. All neuromuscular blocking agents can be used safely although gallamine crosses the placenta; none interferes with uterine retraction.

Drugs and the Fœtus. A large number of drugs are known to cross the placenta, but seldom is their passage into the fœtus of great clinical importance. Morphine and pethidine are well known to cause respiratory depression of the new-born baby, perhaps by a dual mechanism of reducing placental blood flow and by direct passage into the child.

Sympathomimetic amines and other vasoconstrictors may cause fœtal distress by reducing placental blood supply. They do not enter the fœtus. Extreme hypotension from any cause also results in fœtal anoxia.

---

* Roberts, H., *et al.* (1957). *Lancet*, (*i*), 128.

Women overtreated with antithyroid drugs have given birth to goitrous babies.

Most hypnotic, anæsthetic and chemotherapeutic agents also enter the fœtus in varying amounts,* but probably do no harm.

ANÆSTHESIA IN THE DISEASED AND AGED

(See also p. 440)

The normal response to anæsthesia may be greatly modified by disease or by drugs which the patient is already taking. The possibilities are vast and only some of the more important aspects will be mentioned here.

Respiratory Infections predispose the patient to postanæsthetic pulmonary complications such as collapse or pneumonia. Routine use of antimicrobials probably does not prevent postanæsthetic pneumonia in healthy people. In bronchitic patients chemoprophylaxis may be started immediately before or after operation; it should not be begun days beforehand as this will allow opportunity for resistant strains to become dominant in the lungs.

Irritant inhalation anæsthetics and reduction of respiratory excursion by depression of the respiratory centre should obviously be avoided as far as possible, although postoperative chest complications have little relation to the anæsthetic agent used, being chiefly associated with the site of operation and the incidence of pain, *i.e.* they are due to defective ventilation due to pain and fear of coughing.

Anæsthesia in Cardiac Disease. The aim is to avoid the circulatory stress which is caused by struggling, coughing, laryngospasm and breath holding. Drugs given i.v. should be injected slowly to avoid hypotension, which may occur with very many substances if they are given too fast. Anoxia is obviously harmful. It will be seen that skilled technique rather than choice of drugs on pharmacological grounds is the important factor. If heart failure or arrhythmias are anticipated from the condition of the patient or the nature of the operation, digitalis or quinidine should be begun preoperatively.

Anæsthesia in Hepatic and Renal Disease. Very many drugs are metabolised by the liver or excreted by the kidney so that disease of these organs is liable to lead to increased drug effects. This should be taken into account when selecting drugs and their doses. Protection of the patient from mishap due to these causes can only be achieved if the user knows how a drug is treated in the body.

---

* Young, I. M., Martin, J. D. (1959). *In* British Obstetric Practice. 2nd ed. Ed. E. Holland. London: Heinemann.

Anæsthesia in Diabetes. Ether causes hyperglycæmia by stimulating the sympathetic centre in the brain, it therefore slightly complicates the management of the disease and so is best avoided. Details of preparation of diabetics for surgery are given on pp. 459–460.

Anæsthesia in Thyroid Disease. Nowadays patients are not operated on for hyperthyroidism until the metabolic rate has been controlled by drugs (p. 370). If by some mischance an operation must be performed whilst the metabolic rate is high and a thyroid "crisis" follows, it may be treated by methods employed in anæsthetic hypothermia. Hypothyroid patients are liable to be more sensitive to anæsthetic drugs. Hypothyroidism may be corrected rapidly with tri-iodothyronine.

Anæsthesia in Porphyria. Barbiturates, especially thiopentone, should never be used as they may precipitate a severe attack.

Anæsthesia in Muscle Diseases. Patients with myasthenia gravis are very sensitive to curare but not to decamethonium. Those with dystrophia myotonica may recover less rapidly than normal from central respiratory depression and neuromuscular block. All patients with generalised muscular weakness or disease should be treated with caution.

Raised Intracranial Pressure depresses the respiratory centre and these patients are liable to respiratory failure with central nervous depressants, especially opiates.

Anæsthesia in Adrenocortical Insufficiency. The stress of disease, anæsthesia and surgery evokes a response from the adrenal cortex in normal people. Where there is any deficiency due to disease or to suppression of normal function by prior administration of steroids then the additional needs must be supplied. Since acute adrenocortical insufficiency may lead to irreversible collapse it is better to err in giving steroids unnecessarily than to risk withholding them when they are needed, for it is chronic rather than acute steroid therapy that carries dangers. Any patient with known adrenal insufficiency, or one who is having adrenocortical steroids already, or who has had them in the previous six months, needs an additional 200 mg. cortisone or equivalent of another steroid (preferably i.m.) in the 24 hours before a major operation and an additional 100 mg. twice a day for two days after the operation. The dose may then be reduced to maintenance level over a week. Hydrocortisone sodium succinate may be used i.v. in emergency.

Patients with pituitary or adrenocortical insufficiency are said to be intolerant of central nervous system depressants.

Old Age. Old people are liable to become confused by narcotics, especially by hyoscine, and atropine is usually substituted. Apart from this there are no special problems, but mistakes and overdosage are less easily retrieved in the old and frail than in the young and healthy. In general, elderly patients require smaller doses than the young. Hypotension should be especially avoided as it may lead to cerebral softening due to reduced blood supply.

Childhood. Here again the problems are more technical, physiological and psychological than pharmacological. Premedication is often by barbiturates, orally or by rectum, rather than by morphine or papaveretum with hyoscine, although children in fact tolerate these well. Very little anæsthesia is needed for neonates and they are said to be more sensitive than normal to competitive, and less sensitive than normal to depolarising, neuromuscular blocking agents.

Guide to Further Reading on Anæsthetics, Local Analgesics and Neuromuscular Block

(*1*) Evans, F. T., and Gray, T. C. (Editors) (1958). Modern Trends in Anæsthesia. London: Butterworth.

(*2*) Dundee, J. W. (1956). Thiopentone and Other Thiobarbiturates. Edinburgh: Livingstone.

(*3*) Wylie, W. D., and Churchill-Davidson, H. C. (1960). A Practice of Anæsthesia. London: Lloyd-Luke.

(*4*) Edwards, G., *et al.* (1956). Deaths associated with anæsthesia. A report of 1,000 cases. *Anæsthesia*, **11**, 194.

(*5*) Guedel, A. E. (1951). Inhalation Anæsthesia. A Fundamental Guide. 2nd ed. New York: Macmillan.

(*6*) Duncum, B. M. (1947). The Development of Inhalation Anæsthesia, with Special Reference to the Years 1846-1900. London: Oxford University Press.

(*7*) Graff, T. D., and Phillips, O. C. (1959). Consciousness and pain during apparent surgical anæsthesia. *J. Amer. med. Ass.*, **170**, 2069.

(*8*) Tovell, R. M., *et al.* (1955). A comparative clinical and statistical study of thiopental and thiamylal in human anæsthesia. *Anesthesiology*, **16**, 910.

(*9*) Cannard, T. H., and Zaimis, E. (1959). The effect of lowered muscle temperature on the action of neuromuscular blocking drugs in man. *J. Physiol.*, **149**, 112.

(*10*) McIntyre, A. R. (1947). Curare, its history, nature and clinical use. Chicago University Press.

(*11*) Foldes, F. F. (1960). The pharmacology of neuromuscular blocking agents in man. *Clin. Pharmacol. and Therap.*, **1**, 345-395.

(*12*) Evans, F. T., and Gray, T. C. (Editors) (1959). General Anæsthesia. Vol. I. Basic Principles, Vol. II. Techniques, special fields and hazards. London: Butterworth.

Chapter 8

ANALGESICS, PAIN, RHEUMATISM

PAIN AND ANALGESICS

ONE of the greatest services a doctor can do his patients is to acquire skill in the management of pain.

> . . . For what avails
> Valour or strength, thought matchless, quelled with pain,
> Which all subdues, and makes remiss the hands
> Of mightiest? Sense of pleasure we may well
> Spare out of life perhaps, and not repine,
> But live content—which is the calmest life;
> But pain is perfect misery, the worst
> Of evils, and, excessive, overturns
> All patience.*

When the cause of pain cannot be removed, drugs acting on the central nervous system are generally used to relieve it.

For therapeutic purposes, pain may be considered a dual phenomenon, one part being the perception of the sensation and the other the patient's emotional reaction to it.

Drugs may therefore give relief in two ways, first by reducing the ability of the patient to perceive the sensation of pain, probably by an action on the thalamus, or second, by altering the appreciation of the sensation so that it is no longer unpleasant, probably by an action on the cerebral cortex. It is likely that any drug which has the second property is capable of inducing addiction.

The ideal analgesic would be one which is perfectly effective by the first mechanism, and which has no other effects at all. Unfortunately all the most potent drugs act in both ways so that although pain may be relieved, the patient cannot be considered to be mentally entirely normal whilst under their influence.

The pain threshold itself is not independent of the emotional state of the subject. Anxiety has been shown to lower, and relief of anxiety or anger to raise, the pain threshold. Thus although barbiturates are not used as analgesics, they are slightly more effective than dummy tablets in relieving pain and this is probably due to relief of or anxiety to alteration in what Beecher calls the "psychic processing" of the sensation. Dummy tablets or injections have long been known to be effective remedies for pain, giving relief usually to about 40% of cases, but with the disadvantage that they rapidly lose effect with repetition.

---

* JOHN MILTON. Paradise Lost. Book 6. 456-464.

The personal significance of an injury to the subject also modifies the pain threshold. "To the wounded soldier who had been under unremitting shell fire for weeks, his wound was a good thing (it meant the end of the war for him) and was associated with far less pain than was the case of the civilians who considered their need for surgery a disaster" (*1*). The desire for analgesics was far less amongst victims of battle injuries than amongst comparable civilian injuries (*2*). On the other hand morphine has been found to be relatively ineffective against experimental pain in man probably because it acts chiefly against pain which has emotional significance for the patient and less on other pain. This is one reason why experimental pain in man has proved to be virtually useless for assessing the potential clinical value of analgesics which act partly on the psychic response to pain.

New analgesics have been successfully developed by animal testing, possibly because the emotional response to experimental pain in an animal is akin to the human response to disease or accidental injury. This response does not occur in a subject who has volunteered to undergo laboratory experiments which he can end at any time.

When a drug has been found to raise the threshold of response to the measured application of heat, electric shock or local pressure in animals and is thought to have reasonable prospect of being an improvement on existing analgesics, it can only be reliably evaluated in man by trial on patients suffering from the pain of disease. This is often done, with drugs of the morphine type on the postoperative pain of abdominal surgery, and with drugs of the aspirin type on chronic rheumatic conditions. Toxic effects are, of course, simultaneously recorded and taken into account when deciding the clinical utility of a drug. Since what is being measured is how the patient *says* he feels, very careful precautions must be taken if a reliable result is to be obtained. The trial must be double-blind, unless the drug is very new and thought to be dangerous, when it should be made double-blind as soon as possible. Observers who interrogate the patients for relief and side-effects must be constant and trained. It has been found, for example, that if asked by a personable young woman a higher proportion of patients admit to pain relief than if the same question is put by a man.

The necessity for the utmost care in design of drug trials and the interpretation of the results is well shown by the following experiment (*9*):

One physician, using the double-blind technique, treated patients suffering from joint pain with aspirin and with dummy tablets. The patients filled in report cards after two weeks, analysis of which showed that they could not distinguish between the effect of aspirin and the dummy (or placebo). A second physician performed a similar study, also double-blind, in which the patients were interviewed by an observer at their bedside, who recorded the development of analgesic effect. The analysis of the records of this experiment showed that the patients distinguished between aspirin and the dummy tablets, and that these results were "highly significant statistically", that is the results were unlikely to be due to chance, which is all that this expression means. It does not mean that the results *cannot* be due to chance. The question now arises which result should be accepted. The second may be taken as reliable, partly because it accords with general clinical experience over 50 years, although this is by no means infallible, and partly because it is well known that memory for pain is bad, so that recollection of pain that occurred days or weeks ago for comparison with pain felt in the present cannot be, and is not, reliable, whereas comparison of the present with, say, half an hour ago can give very consistent results. If a trial of the first kind were done on a new analgesic there would be a risk of missing a useful drug. No amount of care in recording results, no expertise by the statistician, can compensate for such a fault in design, responsibility for which lies with the clinician.

The reliability of clinical methods of measuring analgesic efficacy has been well shown. When one new analgesic was being tried, it was found that the dose required to produce a given amount of relief increased steadily with the age of the drug sample. Enquiry of the makers whether the drug was chemically stable was met by an assurance that it was. The clinical experiments were repeated with the same result, and further chemical investigation revealed that the compound was indeed not stable.

Other support for the reliability of these techniques comes from the facts that similar results are obtained with the same drugs in different centres and that workers have identified "unknown" coded samples (*1*).

Despite all the activity of chemists producing new compounds and of physicians in testing them with greater and greater accuracy it is of interest that it is the alkaloids of opium and one of the first synthetic analgesics, aspirin, that are still pre-eminent in the treatment of pain.

Choice of Analgesic

In general, pain arising from somatic structures (skin, muscles, bones, joints) responds to analgesics such as aspirin and phenacetin which act solely by raising the pain threshold and so are non-addicting. Pain arising from the viscera is most readily reduced by the narcotic analgesics, such as morphine and pethidine which act both on the pain threshold and on the psychic reaction to pain and are drugs of addiction. This distinction is not, of course, absolute and drugs of the opium group, which are the most potent, may be needed for severe somatic pain. Mild pain from any source may respond to the non-addicting analgesics and these should always be tried first. It is generally held that mixtures of these analgesics give better results than higher doses of one drug alone; probably by giving less side-effects for equivalent relief of pain. Innumerable combinations are available, perhaps the most widely used being Codeine Compound Tablets, B.P., which contain aspirin and phenacetin with codeine. The latter drug, although an opium alkaloid, is a comparatively weak analgesic and is virtually non-addicting; it is commonly used for somatic pain.

Pain Due to Spasm of Visceral Smooth Muscle, when severe, requires large doses of the most potent narcotic analgesics, morphine, pethidine, methadone, but these drugs generally cause spasm of visceral smooth muscle and so have a simultaneous action tending to increase the pain. For this reason an anticholine drug such as atropine is usually given simultaneously to antagonise this unwanted effect. Mild pain of this sort can sometimes be relieved by atropine-like drugs alone or in combination with a non-narcotic analgesic.

Spasm of Striated Muscle is often a cause of pain, including some headaches. Treatment is directed at reduction of the spasm in a variety of ways, including psychotherapy, sedation and the use of centrally-acting muscle relaxants such as meprobamate, mephenesin, or zoxazolamine, as well as the non-narcotic analgesics. Local injections of procaine are sometimes useful.

Neuralgias, such as post-herpetic neuralgia, trigeminal neuralgia or causalgia, can present almost insoluble problems. Analgesics often play only a subsidiary part in their management. In severe cases very high doses of non-narcotic analgesics are often reached with little benefit and an almost inevitable demand for narcotic analgesics follows, with the risk of addiction. Surgery and/or psychotherapy may play a large part in management. Sedation during the acute stage of herpes zoster in patients over 55 years may perhaps help to prevent post-herpetic neuralgia.

Chlorpromazine is worth trying in resistant cases. It potentiates analgesics and may possibly have an independent and obscure effect on the patient's mental attitude to pain.

Gelsemium has long been advocated for trigeminal neuralgia. It is usually mixed with a variety of other drugs, sedatives, analgesics and strychnine. The total absence of any scientific evidence of therapeutic effect does not prove that it has none, but it may be doubted whether gelsemium provides more than a placebo-effect.

Posterior pituitary extracts and cyanocobalamin injections have been advocated for the pain of herpes zoster. Evidence in their favour is very weak indeed.

Thalamic Pain commonly fails to respond to analgesics. Chlorpromazine may be worth trying.

The Pain of Inflammation commonly responds to non-narcotic analgesics.

The Pain of Wounds usually requires narcotic analgesics but the "suffering" of wounds and shock is often best relieved by a barbiturate (*10*).

The Pain of Peripheral Vascular Insufficiency should be treated with non-narcotic analgesics. Narcotic analgesics may be needed eventually. Vasodilator drugs may help but also may be quite ineffective.

The Pain of Malignant Disease may require potentiation of narcotic analgesics by chlorpromazine. Good results have also been claimed with combinations of amphetamine or bemegride with morphine. Higher doses may be reached with less depression and it is possible that the development of tolerance may be delayed.

Headache originating inside the skull may be due to traction on, or to distension of, arteries arising from the circle of Willis, or to traction on the dura mater. Headache originating outside the skull may be due to muscle spasm or to arterial distension. It may also be a referred pain from, for example, the teeth or paranasal sinuses. Treatment by drugs is directed to relieving the muscle spasm, producing vasoconstriction (ergotamine) or else in simply administering analgesics beginning, of course, with the non-narcotics. Combinations of analgesics with caffeine are said to be especially effective in tension headache.

Migraine. The pain of migraine is due to pulsation of the extracranial arteries which have become dilated. The cause is not known and so cannot be removed, but constriction of the vessels by drugs usually relieves the pain.

Ergotamine tartrate is the most effective drug, but often patients prefer the disease to the side-effects of the drug, malaise with nausea and vomiting. A general account of ergot begins on p. 360.

The earlier in the attack that drug therapy begins the more effective it is likely to be. The most effective treatment is ergotamine tartrate 0·1 to 0·5 mg. i.m., repeated as necessary, with a maximum of 1 mg. in 24 hours. If given i.v. the maximum 24-hour dose should be 0·5 mg. If used orally 3 mg. is taken sublingually and followed by 1 to 2 mg. in a few hours up to a maximum of 10 mg. in 24 hours. When ergotamine is highly effective it is sometimes worth teaching a patient to give himself i.m. injections.

Overdose is liable to cause gangrene of the extremities. The drug should be avoided in pregnancy and used cautiously in obliterative vascular disease and hepatic insufficiency. Ergometrine and dihydroergotamine are sometimes effective in migraine; they are less powerful vasoconstrictors and can be safely tried in patients with obliterative vascular disease. Other vasoconstrictor agents, amphetamine, ephedrine and caffeine are occasionally useful. Preparations of ergotamine plus caffeine are perhaps the most effective oral therapy (Cafergot tablets contain ergotamine tartrate, 1 mg., and caffeine, 100 mg; Migril tablets contain ergotamine tartrate, 2 mg., caffeine, 100 mg., and cyclizine hydrochloride, 50 mg.). Ergotamine suppositories are available for use in cases where there is vomiting. Anti-emetic drugs may also be useful. Ergotamine is useless as prophylaxis against migraine, but sedation (phenobarbitone) sometimes helps.

In addition to these drugs analgesics are used (A.P.C. Tablets which contain aspirin, phenacetin and caffeine or Codeine Compound Tablets, or aspirin or paracetamol) and these are often adequate for the milder cases. Attention to detail in the treatment of migraine is well repaid. General aspects of treatment are often more important than are drugs, e.g. psychotherapy, modification of way of living. Sometimes ergot, whilst giving relief, appears to increase the frequency of attacks. Occasional therapeutic success has been claimed with a variety of hormones and during pregnancy.

Dysmenorrhœa, see pp. 356–357.

Miscellaneous. Inhalation of trichloroethylene, as in obstetrics, may be used temporarily for severe intermittent pain when other drugs fail, in, for instance, urinary lithiasis or trigeminal neuralgia.

Procaine infusions i.v. have been used for pain associated with muscular spasm, as in prolapsed intervertebral disc. The risk of convulsions is great. It is probable that this treatment is never essential. Local application of heat and counter-irritation is not to be despised in some cases of musculo-skeletal pain.

The use of cobra venom had a short vogue. It may not have any genuine analgesic power at all and probably acts entirely by an exceptionally powerful placebo effect, the value of which does not outweigh its undoubted toxicity. It is now only used by physicians who wish to astonish their patients.

The general principle that the best treatment of a symptom is the removal of its cause is well exemplified in the routine treatment of the pain of peptic ulcer, for which analgesics are not used.

NARCOTIC OR OPIATE ANALGESICS

> "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."
>
> Thomas Sydenham, 1680.

It is not known when opium was first procured and used as a drug, but it was certainly in prehistoric times, and medical practice always has leaned and still does lean heavily on its alkaloids, using them as analgesic, tranquilliser, antitussive and in diarrhœa. Opium is obtained by incising the seed heads of the opium poppy, allowing the exuded juice to dry for 24 hours and then collecting it. A good yield of opium requires greater sunshine than is usual in Britain, although the plant will grow here, and this also applies to Indian hemp (cannabis indica, marihuana).

Crude opium alone was used in medicine until 1803, when the principal active ingredient was isolated by Friedrich Sertürner who tested the separate fractions he extracted from it on animals and proceeded to try pure morphine on himself and three young men. He observed that the drug caused cerebral depression and spasms of the extremities and that it relieved toothache. He named it morphine after Morpheus the god of sleep.

Opium is still occasionally used, as a pill or as an alcoholic solution (tincture) for arresting diarrhœa (Chalk and Opium Mixture, B.P.C.) and as Dover's powder, which is nowadays made as a tablet (Ipecacuanha and Opium Tablet, B.P.) to promote sweating and sleep in trivial fevers, but pure substances are now preferable as they are more reliable.

The originator of Dover's powder, Captain Thomas Dover, devised it when he retired into general practice from a career as licensed pirate, during which, in 1709, he rescued Alexander Selkirk (Robinson Crusoe) from his island. Dr. Dover combined the two ingredients so that an overdose of opium would be accompanied by an emetic dose of ipecacuanha. This type of built-in safety device has recently been revived in other connections and hailed as a new idea. Dr. Dover's notion of how his powder should be used has been modified greatly, and the formula slightly. He administered 2 to 4 G. in a "white wine Posset" of which he advised the patient to drink a further 2 to 4 pints. Nowadays 0·3 to 0·6 G. is considered sufficient, and no Posset.

Opium contains many alkaloids, but the only important ones are morphine and codeine, although two others, noscapine (narcotine) and papaverine, are occasionally used. In general, morphine is used now where opium was used in the past; its effects differ little from those of opium. However, purified preparations of mixtures of opium alkaloids are available.

Morphine will be described in some detail and other opiate analgesics in so far as they differ from it.

The principal actions of morphine may be summarised:—

ON THE CENTRAL NERVOUS SYSTEM:

a. Depression, leading to: analgesia,
respiratory depression,
depression of cough reflex,
sleep.
b. Stimulation, leading to: vomiting,
miosis,
hyperactive spinal cord reflexes, some only,
convulsions (very rare).
c. Euphoria and addiction (p. 160).

SMOOTH MUSCLE STIMULATION:

a. gastro-intestinal muscle spasm (delayed passage of contents with constipation),
b. biliary tract spasm,
c. renal tract spasm.

Morphine on the Central Nervous System

Morphine is the most generally useful narcotic analgesic, relieving pain in the ways described on p. 151. It both stimulates and depresses the central nervous system. It induces a state of relaxation, tranquillity and euphoria, sleepiness, inability to concentrate and great lethargy, always supposing that this pleasant state is not destroyed or prevented by nausea and vomiting, more common if the patient is ambulant, and excitement. The latter state is unusual but especially prone to occur in horses and cats, and perhaps in women. Generally morphine has a useful hypnotic effect. Morphine depresses the respiratory centre, a particularly undesirable effect in patients with depressed respiration from any cause, but one which is advantageous in the emergency control of paroxysmal nocturnal dyspnœa, when it relieves the frightening respiratory distress by rendering the centre insensitive to the afferent stimuli coming from the lungs. The respiratory depressant effect is antagonised by atropine so that the pair are especially suited for use in anaesthetic premedication. Morphine also suppresses cough by a central action. Morphine stimulates the third nerve nucleus causing miosis (pin-point pupils are characteristic of poisoning, at therapeutic doses the pupil is merely smaller). The chemoreceptor trigger zone of the vomiting centre is stimulated, causing nausea and vomiting, a common side-effect which can be dangerous in patients who have had gastric operations, a cataract removed, or severe myocardial infarction, as well as being unpleasant, although the psychic effects may mitigate this. Some spinal cord reflexes are also stimulated and so morphine is considered unsuitable for use in tetanus and convulsant poisoning; indeed morphine can itself rarely cause convulsions.

Morphine on Smooth Muscle

Alimentary Tract. Morphine acts peripherally on the smooth muscle of the alimentary tract causing it to contract. Peristalsis is simultaneously reduced. Thus although morphine "stimulates" smooth muscle, constipation occurs, with the intestine in a state of tonic contraction. The central action of the drug probably also leads to neglect of the urge to defæcate. Delay in the passage of the intestinal contents results in greater absorption of water which contributes to the constipation.

The Intrabiliary Pressure may rise substantially after morphine, due to spasm of the sphincter of Oddi. It has been measured in man by attaching a manometer to biliary fistulæ in patients who have undergone surgery (5). Sometimes biliary colic is made worse by morphine, presumably in a patient in whom the dose happens to be adequate to increase intrabiliary pressure, but insufficient to produce more than slight analgesia. Another result of this action of morphine is to hold back the pancreatic juice and so to cause a rise in the serum amylase concentration. Morphine and allied drugs are therefore best not used in cases of pancreatitis.

The Ureters contract and renal colic, though usually relieved, may occasionally be made worse as in the case of biliary colic. Micturition may be delayed due to spasm of the bladder sphincter.

Bronchial Muscle is constricted, but so slightly as to be of no importance, except perhaps in asthmatics in whom morphia is best avoided anyway because of its respiratory depressant effect.

Whenever morphine is used and the smooth muscle effects are objectionable, atropine should be given simultaneously, for it antagonises spasm although it does not restore peristalsis. Unfortunately it does not effectively oppose the rise of pressure induced by morphine in the biliary system.

Other Properties of Morphine

Increased sweating usually, and pruritus and pilo-erection sometimes, occur. Postural hypotension is not uncommon and the blood pressure may be lowered by morphine in cases of peripheral circulatory failure. Morphine tends to prolong labour. It is well absorbed from the alimentary tract, but not from the mouth, and not at all from intact skin. It is commonly given s.c. when speed and certainty are desired, and acts in a few minutes and lasts for 4 to 6 hours. Morphine is a standard tranquilliser for shocked patients, but there may be intense peripheral vasoconstriction which can delay absorption for hours, so that a second or even third dose may be injected before the patient has absorbed the first and so lead to poisoning when the vasoconstriction passes off. In such cases morphine should be given i.m. or slowly i.v. Morphine is detoxicated in the liver and excreted in the urine. The restlessness of severe cases of hepatic failure may occasionally demand morphine when other drugs have failed but it should be given in very small doses. In such patients it would seem reasonable to try barbitone first and then other barbiturates, chloral or paraldehyde. Despite the fact that some of these are metabolised by the liver they are less potent respiratory depressants than morphine and so are safer.

Uses of Morphine

The important uses of morphine and its allies are:—

1. to relieve pain
2. to relieve anxiety in serious and frightening disease, *e.g.* shock, hæmatemesis or heart failure
3. to control diarrhœa
4. as premedication for surgery
5. to control cough
6. for dyspnœa in acute left ventricular failure (paroxysmal nocturnal dyspnœa)
7. to control restlessness, rarely
8. to produce euphoria in the dying

Any of these desirable effects may be interfered with by morphine-induced vomiting.

Tolerance to Morphine occurs with continued frequent use of morphine and there is cross-tolerance with chemically related drugs and pethidine. The tolerance may reach a very high degree, an exceptional addict taking 600 mg. or more several times a day. An average addict is more likely to take about 300 mg. Duration of tolerance after cessation of administration is variable for different actions, from a few days to weeks. Little is known about it. Children are often said to be naturally intolerant of morphine, but this is not true and it is invaluable in heart failure in children (maximum dose s.c. 0·2 mg./Kg.). The aged should be given small doses only.

Addiction to Morphine

Morphine is one of the drugs most widely used by addicts. Opium addiction seems to be very much less disabling than morphine addiction. It is said, and there is reasonable support for it, that the use of opium by Eastern peoples presents little more serious a social problem than the abuse of alcohol by Western peoples. All are agreed however that addiction to the pure alkaloids causes results so detrimental to society that the community cannot allow such misuse to go unchecked.

The typical withdrawal syndrome in a morphine addict consists largely of effects which are opposite to the normal pharmacological actions.

"When an addict misses his first shot, he senses mild withdrawal distress ('feels his habit coming on') but this is probably more psychological than physiological, for fear plays a considerable role in the withdrawal syndrome. At this stage a placebo may give relief. During the first 8 to 16 hours of abstinence the addict becomes increasingly nervous, restless and anxious; close confinement tends to intensify these symptoms. Within 14 hours (usually less) he will begin to yawn frequently; he sweats profusely and develops running of the eyes and nose comparable to that accompanying a severe head cold. These symptoms increase in intensity for the first 24 hours, after which the pupils dilate and recurring waves of goose flesh occur. Severe twitching of the muscles (the origin of the term 'kick the habit') occurs within 36 hours and painful cramps develop in the backs of the legs and in the abdomen; all the body fluids are released copiously; vomiting and diarrhœa are acute; there is little appetite for food and the addict is unable to sleep. The respiratory rate rises steeply, both systolic and diastolic blood pressure increase moderately to a maximum between the third and fourth day; temperature rises an average of about one degree, subsiding after the third day; the blood sugar content rises sharply until the third day or after; the basal metabolic rate increases sharply during the first 48 hours. These are the objective signs of withdrawal distress which can be measured; the subjective indications are equally severe and the illness reaches its peak within 48 to 72 hours after the last shot of the opiate, gradually subsiding thereafter for the next 5 to 10 days. Complete recovery requires from three to six months with rehabilitation and, if needed, psychiatric treatment. The withdrawal syndrome proper is self-limiting and most addicts will survive it with no medical assistance whatever (this is known as kicking the habit 'cold turkey'). Abrupt withdrawal is inhumane, but with the development of such drugs as methadone, it is possible to reduce the distress of withdrawal very considerably".*

It is usual to cover the withdrawal period (about 10 days) with morphine-like drugs or with chlorpromazine and barbiturates. Withdrawal symptoms occur in infants born to addicted mothers. There is a risk of making patients morphine addicts if prolonged treatment is given (the more widely the doses are spaced the less the risk), and whilst this may not be very seriously regarded in those who are dying, it can present a serious problem in, for example, patients with trigeminal neuralgia or recurrent urinary lithiasis. It is impossible to give any rule as to how quickly a patient can become addicted.

---

* From Maurer, D. W., and Vogel, V. H., 1954. Narcotics and Narcotic Addiction: courtesy of Charles C. Thomas, publisher. Springfield, Ill.

Toxicity of Morphine

Death from overdosage is due to respiratory depression. The blood pressure is usually well maintained, if the patient is supine, until anoxia causes a state of shock. At this point the pupils, whose small size is a useful diagnostic indicator, may dilate. Correct diagnosis is vital, for nalorphine (5 to 10 mg. i.v. or i.m.) is a specific antidote. Nalorphine has a powerful antagonistic effect against the respiratory depression, lasting two to three hours, which is shorter than the duration of action of the morphine so that the nalorphine may have to be repeated. Arousal from coma does not usually occur in man, although nalorphine restores consciousness in some animals. Overdose with nalorphine may actually increase the respiratory depression due to morphine. In addicts nalorphine induces a typical withdrawal syndrome and so it should be used cautiously. Respiratory stimulant drugs are not ordinarily required. Picrotoxin should not be used because its effects are synergic with the stimulant effect of morphine on the spinal cord and promote convulsions. Apart from nalorphine the general treatment is the same as for overdose by any cerebral depressant drug.

Preparations of Opium and its Derivatives

Chloroform and Morphine Tincture (B.P.C.), or chlorodyne, 0·3 to 0·6 ml. orally, is useful in diarrhœa. Tincture of Opium (laudanum), 0·3 to 2 ml., is used in enemas to relieve diarrhœa in severe ulcerative colitis and orally to control diarrhœa and cough for short periods. Nepenthe is a proprietary liquid preparation of opium that can also be injected, but there is no good reason for using such preparations when pure drugs are available whose pharmacology is better understood. Squill Opiate Linctus, B.P.C., or Gee's linctus, is used in cough. The squill, a digitalis-like glycoside, is included to act as an irritant expectorant. Squill is also used as a rat poison. Gee's linctus is a popular antitussive, but probably no more effective than the opium alone. Papaveretum (Omnopon), 10 to 20 mg., can be given by any usual route. It is a pure preparation of opium alkaloids. It is said to cause less vomiting than morphine for equal analgesia and is widely used, although the advantage claimed has not been proved. Ipecacuanha and Opium Tablets, B.P., Dover's Powders, are described on p. 157. Morphine sulphate, 10 to 20 mg., can be injected by any usual route or given orally.

There are numerous other preparations including Kaolin and Morphine Mixture, B.P.C., and Morphine Suppositories, B.P.C.

Codeine

Codeine (methylmorphine) has similar properties to morphine but is only one-quarter to one-sixth as potent an analgesic. Most of its other actions are only about one-tenth that of morphine so that codeine is a valuable analgesic although it is inadequate against very severe pain, however much is given. But it differs from morphine qualitatively in one respect; large doses cause excitement not narcosis. It is widely used as an analgesic, antitussive and anti-diarrhœal agent in a dose of 10 to 60 mg. of codeine phosphate orally. It is seldom given by injection, more potent drugs being then preferred. There are numerous preparations including Codeine Compound Tablets, B.P., and Codeine Linctus, B.P.C. Large doses of codeine (60 mg.) are commonly needed to control cough. Addiction can occur but is rare. Despite their name much of the effect of Codeine Compound Tablets, B.P., is due to the aspirin (250 mg.), and phenacetin (250 mg.) rather than to the relatively small amount of codeine (8 mg.).

Pethidine (Meperidine)

Pethidine was introduced in 1939, it is related to atropine and was synthesised for its possible smooth muscle relaxant properties. When given to mice it caused the tail to stand erect, a characteristic of morphine-like drugs which is thought to be due to spasm of the anal sphincter. This attracted attention and pethidine was examined for analgesic power.

Pethidine cannot relieve such severe pain as can morphine but is effective against pain beyond the reach of codeine. Despite its substantial chemical dissimilarity to morphine, pethidine has many similar properties including that of being antagonised by nalorphine.

Pethidine differs from morphine in the following respects:—

It does not suppress cough usefully.
It does not cause constipation, but its effect in the upper small intestine is similar to morphine and there is spasm of the sphincter of Oddi.
It does not cause spasm of the smooth muscle of renal tract or bronchi.
The pupils are not constricted.
It has little hypnotic effect.
It seldom causes vomiting.

There is disagreement as to the extent to which pethidine depresses respiration. It is probable that in equianalgesic doses it is as depressant as morphine. Death from overdose is due to respiratory depression. Pethidine can cause tremors and convulsions.

Addiction to pethidine occurs, with some tolerance, especially to the side-effects, but its psychic effects are less constant and less marked than those of morphine. It is metabolised in the liver. Pethidine has evident advantages over morphine for pain which is not very intense, and is widely used. It is usually given as the hydrochloride orally (50 to 200 mg.) or i.m. (50 to 150 mg.), when its effects last three to four hours. The solution is irritant and so it is not given s.c. Given i.v. (50 to 100 mg.) it is used sometimes in anæsthetic practice to provide a state of "general analgesia". It is widely used in obstetrics.

Methadone (1946)

Methadone is a synthetic drug chemically and pharmacologically similar to morphine. It is less hypnotic and perhaps it causes less respiratory depression. It is more reliably effective when given orally than is morphine. Vomiting is fairly common, especially if the patient is ambulant. 5 to 10 mg. of hydrochloride are given about 4-hourly orally or s.c. Addiction occurs.

Diamorphine (Heroin)

Heroin is a semisynthetic drug first made from morphine at St. Mary's Hospital, London, in 1874. It was introduced in 1898 as a remedy for cough and for morphine addiction and is very effective against both. Some years passed however before it was appreciated that it "cured" morphine addiction by substituting itself as the addicting agent. Since then it has become a popular opiate drug with addicts and has achieved such a reputation that it is difficult now to discover whether addicts are attracted to it because it is pleasanter or because of its reputation, plus its availability from drug peddlars in some countries.

It is commonly stated that heroin is the "most potent" drug of addiction existing but there is no good evidence for this and a modern authority has questioned whether it has greater liability to cause addiction than has morphine (*3*). It has also been reported that some addicts have voluntarily preferred methadone to heroin and it is probable that heroin has no especial pharmacological potency in this connection.

In almost every country the manufacture of heroin, even for use in medicine, is now illegal. The first to try this prohibition as a remedy for widespread drug addiction was the U.S.A. which banned heroin manufacture in 1924, provoked by the magnitude of their addiction problem and not then discouraged by their experience with alcohol prohibition (1919 to 1933). Such an approach to the illicit traffic in general and heroin in particular is almost certainly futile, for contraband heroin has hardly ever been legally manufactured heroin which has been diverted to illegal uses. It is heroin made by a simple process from smuggled opium or morphine. The solution to the spread of heroin addiction evidently lies in the suppression of illegal opium traffic, not in stopping legal manufacture of heroin.

When in 1953 the British Government proposed to follow suit with a similar prohibition of heroin in medical practice (*2*) it was pointed out that British legally manufactured heroin had never contributed to the international illicit drug traffic, so that, whether or not the drug was useful in therapeutics, a ban on its use by the medical profession was pointless in that it would not deprive addicts. This reasonable argument was lost in a flood of vigorously expressed opinion on the advantages of heroin which was based solely on clinical impressions. These opinions, unsupported as they were by any scientifically obtained data, together with the fact that in the U.S.A. patients, though not addicts, had been without heroin for 21 years, did not form an impressive body of evidence in favour of retaining heroin solely on grounds of clinical necessity.

Even now, after heroin has been in use for over 60 years, it is still not known for certain whether it has unique therapeutic properties. If it has, they are slight, but not necessarily trivial. The important fact is that the illicit drug traffic is none the worse for the banning of heroin from medicine. Heroin is still available to doctors in Britain, but is no longer exported.

Heroin is a powerful euphoriant, analgesic, cough and respiratory depressant, and perhaps causes less vomiting than morphine, and greater euphoria with less sleepiness, otherwise its properties are those of morphine. It is used chiefly to control severe pain and cough and to comfort the dying. It is, like morphine, a powerful drug of addiction and so should be employed with due regard to this hazard. The initial oral dose of heroin hydrochloride is 5 to 10 mg. or s.c. 3 to 6 mg.

Noscapine (narcotine)

Noscapine has antitussive effect, but little else, it is said to be non-addicting and can be used instead of codeine. It does not constipate, is not narcotic and, like papaverine, is only included here because it is an alkaloid of opium.

Papaverine

Papaverine differs from the more important opium alkaloids. It relaxes smooth muscle throughout the body, especially in the vascular system. It has never found a wide application in therapeutics, perhaps because its action is unreliable and brief, although it is sometimes advocated in angina pectoris and peripheral vascular disease. The oral dose of the hydrochloride or sulphate is 60 to 200 mg. and 30 to 60 mg. may be given i.m. It is occasionally injected into an area where local vasodilatation is desired, especially into and around arteries and veins to relieve spasm during vascular surgery and when setting up i.v. infusions.

OTHER ANALGESIC AND ANTITUSSIVE DRUGS RELATED TO MORPHINE

Name	*Oral dose*	*Antagonised by nalorphine*	*Remarks*
dextromethorphan (Romilar)	15–30 mg.	no	Used as a syrup in cough, similar to codeine but fewer side-effects. No significant respiratory depression.
hydromorphone (Dilaudid)	2·5–5 mg. (2 mg. s.c.)	yes	Shorter action than morphine, otherwise similar.
hydrocodone (Dicodid)	5–15 mg.	probably	Similar to codeine but more effective, a useful antitussive.
dihydrocodeine (D.F. 118)	20–50 mg.	yes	Few side-effects. A little less effective than morphine.
alphaprodine (Nisentil)	(40–60 mg. s.c.) (20–30 mg. i.v.)	yes	Used by injection for rapid and brief (2 hr.) analgesia.
anileridine (Leritine)	(25–50 mg. s.c.)	yes	Similar to pethidine.
methyldihydromorphinone (Metopon)	3–6 mg.	yes	Similar to morphine.
levorphanol (Dromoran)	2–3 mg. (2–3 mg. s.c.)	yes	Differs insignificantly from morphine.
phenadoxone (Heptalgin)	25–50 mg. (5–10 mg. s.c.)	yes	Similar to methadone but unreliable orally.
pholcodeine (Ethnine, Memine)	5–15 mg.	no	Used for cough only, less constipating than codeine. Insignificant respiratory depression.
dipipanone (Pipadone)	12·5–25 mg. (12–20 mg. i.m.)	yes	The tablets commercially supplied contain cyclizine to reduce vomiting.
dextromoramide (Palfium)	5–20 mg. (5–15 mg. s.c.)	yes	Similar to morphine. May constipate less.

The doses given are those of the commonly used salts. All the drugs are chemically related to morphine. Since they are rather irritant in solution and, like morphine, release histamine in the tissues they are better given by deep s.c. injection or even i.m., when not given orally. For most, if not all, claims of substantial superiority have been made. The continued wide use of codeine and morphine is sufficient answer to many of them.

Ethylmorphine (Dionin)

Ethylmorphine is used only for its powerful irritant effect, *e.g.* when put on the eye, in which it causes a great increase of blood flow in the deep and superficial vessels. A 1% solution of the hydrochloride is sometimes used in iritis and corneal ulcer for this purpose.

Narcotic Antagonists

Nalorphine (N-allylnormorphine)

The antagonistic effect of a related substance on opiate-induced respiratory depression was described in 1915, but the opportunity of introducing a specific antidote into clinical practice was not taken until 35 years later.

Nalorphine is closely related to morphine and has weaker but similar effects, except that it does not cause constipation. It antagonises morphine probably by competing with it at the site of action; it is not itself an analeptic agent and so it does not oppose other respiratory depressants such as the barbiturates, which are not chemically related to it. Antagonism is unequal for all the effects of morphine, for example it seldom awakens subjects from morphine-induced coma. High doses of nalorphine cause respiratory depression.

Attempts to use morphine-nalorphine combinations to obtain analgesia without any of the disadvantageous side-effects of morphine have not been notably successful despite the fact that nalorphine itself is an effective analgesic.

Nalorphine antagonises all morphine-like drugs and pethidine; it induces the withdrawal syndrome in addicts to these drugs, and this can be dangerous. For dosage see p. 162.

In obstetrics, when morphine or pethidine has been given to the mother, there is a risk of respiratory depression in the child at birth. This can be prevented by giving nalorphine hydrochloride to the mother (5 to 10 mg. i.m. or i.v.) before birth, or to the child at birth (0·2 to 0·5 mg. into the umbilical vein).

Levallorphan is chemically to levorphanol (see table, p. 166) what nalorphine is to morphine. It has similar properties and uses. In opiate poisoning the dose is 0·5 to 1 mg. i.v. repeated as necessary. To a newborn child the dose is 0·05 mg. i.v. Levallorphan-pethidine mixture (Pethilorfan) is used for obstetric (p. 147) and other analgesia.

NON-NARCOTIC OR ANTIPYRETIC ANALGESICS

These are orally active weak analgesics with nothing much to choose between them except that some are more toxic than others. They also have an antipyretic effect and some have an anti-inflammatory or "antirheumatic" action. Habituation to these drugs occurs, but probably not true addiction.

They include:—

Salicylates
Aniline Derivatives: phenacetin, paracetamol, acetanilide
Pyrazolone Derivatives: phenylbutazone, phenazone, amidopyrine

Salicylates

Willow bark, which contains salicin, was used in the 18th century for fever, as a cheap substitute for imported cinchona bark. The latter half of the 19th century saw the first use of sodium salicylate in acute rheumatism and the preparation and introduction of acetylsalicylic acid (aspirin).

The Actions of Salicylates

The manifold actions of salicylates are listed below. The mechanism of most of them is obscure:—

1. Analgesic
2. Antipyretic
3. Anti-inflammatory
4. Respiratory stimulant
5. Metabolic stimulation and insulin-like effect
6. Prevention of uric acid reabsorption in the kidney (uricosuric)
7. Hypoprothrombinæmic
8. Gastro-intestinal disorders

1. **Analgesic Effect of Salicylates.** This is mild, being less than that of codeine. There is no evidence of any effect on the psychic reaction to pain that plays so important a part in the action of the narcotic analgesics. Salicylates are most effective against mild pain of somatic origin.

2. **Antipyretic Effect of Salicylates.** In fever the body temperature rises chiefly because of a reduction in heat dissipation, and salicylates act on the temperature regulating centre causing an increase in heat dissipation by peripheral vasodilation and sweating. There is evidence in man that there is concurrent mobilisation of body water which shows itself as increased plasma volume and lower hæmatocrit. This water is available for sweating. Nowadays, when antipyretics are very seldom used for the purpose implied by their name there is less interest in the problem, but before chemotherapy existed the physician could often do nothing else to show his power over disease. Nowadays the efforts previously devoted to reducing fever are turned more profitably to removing its cause.

Salicylates in therapeutic dose have insignificant effect on normal body temperature. Salicylate poisoning may result in hyperpyrexia (p. [illegible]).

3. **Anti-inflammatory ("Antirheumatic") Effect of Salicylates.** This action is probably independent of the analgesic effect. It may be that salicylates exert their characteristically dramatic effect in acute rheumatism by a combination of water mobilisation from inflamed tissue and an increase in cell metabolism. In addition it may be relevant that salicylates exert an antifibrinolysin effect and interfere with some experimental immunological phenomena.

4. **Respiratory Stimulation** is a characteristic of salicylate intoxication. Its cause is still disputed. The explanation longest in the field is that salicylates directly stimulate the respiratory centre, with resulting respiratory alkalosis due to excessive carbon dioxide loss through the lungs, but this has been challenged with the claim that the hyperventilation is secondary to stimulation of cell metabolism. This increased metabolism particularly involves protein so that less carbon dioxide is produced relative to the oxygen required, thus also accounting for the characteristic initial respiratory alkalosis. The metabolic stimulant effect is undoubted, and as a tour-de-force the basal metabolic rate of thyroid deficient patients has been raised by large doses of aspirin. Attention has been drawn to the paradox of a drug which stimulates metabolism also being an effective antipyretic. Attempts to use salicylates to increase respiration in patients with pulmonary insufficiency and carbon dioxide retention (respiratory acidosis) have not given useful therapeutic results, and if the second explanation of the mechanism is true they may be undesirable.

5. **Metabolic Stimulation by Salicylates** "at cellular level" occurs, as above. Salicylates also have an "antidiabetic" action, reducing the severity of experimental diabetes in animals. In human diabetics this has been confirmed and it has been found possible to replace a substantial amount of insulin by aspirin, although side-effects limit this use. The possibility of making compounds with a greater "antidiabetic" effect and few or no toxic effects exists. At least part of this "antidiabetic" effect may be due to increased peripheral utilisation of glucose which occurs with an increase in metabolic rate.

6. **Renal Tubular Reabsorption of Uric Acid** is reduced and salicylates can be used to deplete gouty patients of uric acid, but very high doses are needed.

7. **Hypoprothrombinæmia Due to Salicylates** occurs with large doses; it is unlikely at less than 5 G. of aspirin or sodium salicylate a day. It is preventable and reversible by vitamin K_1. Severe hæmorrhage is rare. The mechanism of action is unknown.

8. **Gastro-intestinal Disorders Due to Salicylates** (*1, 3, 4*). Hæmorrhage, as evidenced by occult blood in the fæces, has been shown to occur in about 70% of people taking aspirin. This is presumably due to local irritant effect on the mucosa for it occurs at doses below those which alter

prothrombin production. The incidence of bleeding is probably uninfluenced by the form in which aspirin is taken (as tablet, as a suspension, or buffered), however expensive (*1*).

Occasional patients have a florid hæmatemesis on taking aspirin. This is said both to be and not to be an unusual type of hypersensitivity reaction. Much of the nausea, vomiting and epigastric discomfort attributable to salicylates is due to an action in the central nervous system and not to a local effect.

Aspirin is best avoided in patients with disease of the upper gastro-intestinal tract, but any proposal that the drug should be abandoned in favour of newer synthetic analgesics ignores the fact that it has been used successfully for decades by the public and the medical profession, despite microscopic blood loss. Considering that many thousands of tons are consumed annually, significant toxic effects from aspirin are uncommon (*10*).

Salicylates and Adrenocortical Steroids

Similarities between the effects of salicylates and those of adrenocortical steroids, e.g. "antirheumatic" and uricosuric action are common to both, have aroused speculation as to whether salicylates perhaps exert some of their effects by an action on the adrenal cortex. Evidence is conflicting on this point, but it seems more likely that the similarities may be the end result of different processes, for instance adrenocortical steroids cause naturally formed serum antifibrinolysin to increase and salicylates produce the same result by direct inhibition of fibrinolysin. Administration of either leads to reduction in antistreptolysin-O titre in the blood of patients with rheumatic fever.

Absorption, Metabolism and Excretion of Salicylates

Salicylates are well absorbed from the alimentary tract and the rate of absorption is increased if sodium bicarbonate is given simultaneously. However, the rate of excretion of salicylates is higher in an alkaline urine and any increased absorption is more than counterbalanced. The routine incorporation of bicarbonate in salicylate mixtures to reduce toxicity is irrational as the same end is achieved by simply reducing the dose of salicylate. Salicylate is excreted in the urine both unchanged and in combination. About half of a dose is excreted in 24 hours and steady blood levels can be maintained if salicylates are given orally 6-hourly.

Salicylate Preparations for Analgesia

Aspirin (Acetylsalicylic Acid). The dose is 0·3 to 1 G. orally. Aspirin hydrolyses in the presence of water into salicylic and acetic acids; it should therefore be kept dry, and is best not prescribed in watery mixtures as these are only stable for a few days.

Soluble Aspirin Tablets, B.P., contain citric acid and calcium carbonate so that when the tablet is dropped into water the acid and alkali react and cause the aspirin to disperse as a fine suspension. There is now doubt as to whether this is less toxic than plain aspirin.

There are innumerable analgesic tablets containing aspirin with other drugs, including:—

Aspirin and Phenacetin Tablets, B.N.F., containing aspirin (220 mg.) and phenacetin (160 mg.).

Codeine Compound Tablets, B.P., containing aspirin (250 mg.), codeine (8 mg.) and phenacetin (250 mg.).

Aspirin Compound Tablets, B.P.C., (A.P.C. Tablets), containing aspirin (220 mg.), phenacetin (160 mg.) and caffeine (30 mg.).

There are also numerous proprietary preparations.

Toxicity of Salicylates (5); see also p. 169

Hypersensitivity reactions sometimes occur and can be fatal. Urticarial rashes and pruritus are commoner than the much more dangerous asthma and anaphylactic shock.

The typical clinical picture of mild to moderate overdose consists of nausea and vomiting, tinnitus, deafness, hyperpnœa, headache and mental confusion. If administration has been prolonged there may rarely be hæmorrhage due to hypoprothrombinæmia. Presence of occult blood in the fæces is usual.

With a big overdose these symptoms may be followed by mania, hyperpyrexia, convulsions and coma, with severe dehydration and ketosis.

The metabolic changes in salicylate poisoning are complicated and not entirely understood, but have a very important bearing on therapy.

Initially there is a respiratory alkalosis as described above. The blood carbon dioxide level falls, the blood pH tends to rise and tetany may occur. This tendency for the blood pH to rise is combated by the kidney which secretes an alkaline urine, reducing the body pH towards normality. The alkaline urine is produced by reduction of renal tubular reabsorption of bicarbonate, which reduces the plasma bicarbonate and necessarily depletes the body of cations such as sodium and potassium, as well as of water. The reduction in plasma bicarbonate is of no clinical importance in itself but it means that the body is deprived of one of its buffering systems and so may become particularly vulnerable to the next stage in salicylate poisoning (acidosis) which endangers life. The further progress of salicylate poisoning is complicated because many factors operate.

The respiratory alkalosis is replaced by a metabolic acidosis, resulting chiefly from a combination of increased catabolism and dehydration. The metabolic acidosis reduces the plasma bicarbonate still further.

Dehydration is due to loss of water from the respiratory tract, by vomiting and by diarrhœa, as well as through the kidneys. Relatively more water than sodium may be lost so that hypernatræmia may occur.

Hyperpyrexia may also occur. This paradox, of an antipyretic causing fever, is due to a combination of the metabolic stimulating action with defective heat elimination which is inevitable in a dehydrated patient. The antipyretic effect of salicylate is dependent on ability to sweat.

Hyperglycæmia may also occur despite the insulin-like effect of ordinary doses of salicylate. It is probably due to interference with glucose utilisation by toxic doses.

Ketosis occurs in severe cases of poisoning, it is due to the increased catabolism with decreased carbohydrate utilisation as mentioned above and is promoted by the starvation which accompanies the poisoning.

Treatment of Severe Salicylate Poisoning. The most urgent threats to life are commonly dehydration and hyperthermia. Apart from the general treatment of poisoning, severe cases need intravenous therapy. Correction of dehydration also enables the patient to begin sweating to reduce the pyrexia which is meanwhile treated, if necessary, by sponging with water or alcohol.

Blood pH measurements are useful in deciding the stage to which poisoning has progressed since the plasma bicarbonate levels are of no help. In the early stages lactate or bicarbonate solutions are dangerous as they may precipitate fatal tetany. However, they are obviously desirable later when metabolic acidosis has supervened. Moreover, alkalinisation of the urine increases the rate at which the kidney can excrete salicylate. Relief and prevention of dehydration are at least as important. If hypernatræmia has developed then hypotonic solutions are needed. In severe cases the fluid régime suitable for diabetic ketosis is indicated; potassium may be essential, particularly in the later stages.

No attempt should be made to interfere with the hyperventilation of metabolic acidosis as this is a protective mechanism which reduces the fall of blood pH.

Glucose may be given, despite any hyperglycæmia, since starvation contributes to the ketosis.

In an emergency, without the guidance of laboratory measurements, an i.v. infusion of Sodium Lactate Compound Injection, B.P., is the best to begin with.

The similarity between salicylate poisoning and diabetic ketosis can be very close (hyperglycæmia, ketosis and reduction of Benedict's solution by the urine, the latter due both to glucose and to glucuronides of salicylate). Salicylate gives a brighter violet colour with ferric chloride than do ketones, and the colour due to salicylates is not influenced by first boiling the urine, which process removes the volatile ketones and destroys the non-volatile acetoacetic acid present in diabetic ketosis.

Uses of Salicylates

Apart from their use in minor pain and fevers, the principal use of salicylates is in rheumatic fever (p. 175).

Salicylamide is similar to salicylates. Claims that it gives equal therapeutic effect for less toxicity have not been firmly established.

Methyl Salicylate (oil of wintergreen) is too irritant to be used internally. It is used in liniments as a counter-irritant.

Aniline Derivatives

Phenacetin (Acetophenetedin)

Phenacetin is an effective mild analgesic but rather more toxic than salicylates. It is commonly used in combination with other analgesics so that a lower dose can be used. It has antipyretic and analgesic activity but probably less "antirheumatic" effect than salicylates. The dose is 0·3 to 1 G. Acute or chronic over-dosage leads to methæmoglobinæmia with hæmolysis of the red cells. Large doses over a long period may cause a nephritis. Toxic effects due to self-medication by people with chronic pain are fairly common.

There is no specific treatment for phenacetin poisoning.

Phenacetin is converted into *p*-acetamidophenol in the body and this is probably the active analgesic substance.

Paracetamol (Panadol) is the metabolite of phenacetin which provides the analgesia. Very high doses may be capable of causing hæmolysis but, apart from gastro-intestinal upsets, paracetamol is on the whole remarkably free from toxicity and is a useful analgesic. The oral dose is 0·5 to 1 G.

Acetanilide

Acetanilide was introduced into medicine by mistake in 1886. It was intended to treat a pyrexial patient with intestinal worms by naphthalene, but acetanilide was given in error and the patient's temperature fell. It is an effective antipyretic and analgesic and is widely sold in proprietary preparations. It can be regarded as a more toxic form of phenacetin and since it has no compensating advantages it could well be abandoned. It should never be used for more than a few days at a time for it causes methæmoglobinæmia with hæmolysis.

Pyrazolone Derivatives

Phenazone (antipyrine) is little used because of its toxicity which includes rashes, giddiness, tremors and sweating. It has no advantages to compensate for these.

Amidopyrine is perhaps the most effective of the antipyretic analgesics, but it is dangerous and should never be used. The principal toxic effect is agranulocytosis. Proprietary preparations containing it under various names still exist.

Phenylbutazone (Butazolidin)

Phenylbutazone was used as a solvent for amidopyrine injections. In 1949 it was noticed that, in patients with rheumatoid arthritis, better clinical results were obtained when amidopyrine was given by injection than by mouth, despite the fact that blood levels of the drug were similar in each case. The only difference was the injection solvent (phenylbutazone) and this was then tried alone and found to have potent "antirheumatic" effects and to be a weak analgesic in addition. It is usually given daily by mouth and there is cumulation over about four days. There is no purpose in exceeding the recommended doses, for the blood level does not increase concurrently, due to increased metabolism of the drug with increased dose. The blood level with 1600 mg. and 800 mg. a day are the same, but toxic effects increase with the dose. 800 mg. a day can be given without great risk for a short time in many patients if they are watched carefully. Generally it is undesirable to exceed 400 mg. a day. The daily total of phenylbutazone is usually given in three or four doses. Phenylbutazone is also useful in ankylosing spondylitis.

Phenylbutazone prevents renal tubular reabsorption of urate and is used for this as well as for its anti-inflammatory (antirheumatic) and analgesic effects in acute gout. Its anti-inflammatory effect can be useful in superficial vein thrombosis and perhaps giant-cell arteritis. Some deny any anti-inflammatory effect and attribute all benefit to analgesia. Like other uricosuric agents, phenylbutazone, in low dose, may actually cause retention of uric acid. This can be masked by hæmodilution due to salt and water retention (see below).

Toxic effects are common except at low doses, and can be fatal. They include gastro-intestinal upsets with perforation of peptic ulcers, hæmatemesis and melæna.

Œdema occurs due to a renal effect in reducing sodium and water excretion and this may precipitate heart failure. Rashes, vertigo, insomnia, visual disturbance and agranulocytosis or aplastic anæmia also occur. Hepatic damage is rare.

Active search continues for compounds with the therapeutic activity of phenylbutazone but without its toxicity.

Innumerable non-narcotic preparations are available, for the market is vast and profitable. No drug of importance has been omitted from the account above.

DRUG TREATMENT OF RHEUMATIC FEVER

So effective are salicylates in relieving pain and inflammation in rheumatic fever that failure to respond within 48 hours throws doubt on the diagnosis. Dispute has long existed about whether the late cardiac and other long-term complications of acute rheumatism can be prevented by salicylates. It now seems likely that they cannot.

From their introduction into therapeutics adrenocortical steroids have been used in rheumatic fever. They also provide dramatic relief and the problem has been to decide whether salicylates or steroids or both together give the best therapeutic result, particularly regarding the prevention of late complications. Enough time has not passed to enable a complete assessment to be made, but evidence is accumulating that it is desirable to use both steroids and salicylates.

Illingworth and his colleagues (6) have compared five different treatments on a total of 200 patients against an untreated group:—

Group 1 had no specific treatment
,, 2 ,, low doses of sodium salicylate
,, 3 ,, high doses of sodium salicylate
,, 4 ,, adrenocortical steroids or corticotrophin
,, 5 ,, adrenocortical steroids plus low doses of sodium salicylate
,, 6 ,, adrenocortical steroids plus high doses of sodium salicylate

They have concluded that the best treatment is adrenocortical steroids plus high doses of salicylates. The benefits conferred are a more rapid fall of the erythrocyte sedimentation rate (E.S.R.), a shorter duration of arthritis, new rheumatic manifestations during treatment are fewer, temperature falls sooner and more cardiac murmurs disappear.

Rheumatic fever may be treated initially with oral sodium salicylate 150 to 200 mg. per Kg. body weight total per day divided into four doses until the serum salicylate level is 30 to 40 mg./ml. at which level it should be maintained by adjusting the dose. If it is not possible to measure serum salicylate levels then the maximum tolerated dose should be used. If there is heart failure aspirin is used, to avoid giving sodium. Bicarbonate should not be given with the salicylate as it simply increases the turnover.

In addition an adrenocortical steroid should be given, say prednisone, 60 mg. on the first day, then 40 mg. a day for four days, 20 mg. a day for 16 days, 12·5 mg. a day for the fourth and fifth week and 10 mg. a day for the sixth week and after. Treatment should be continued for three months or until the E.S.R. is normal for three consecutive weeks, whichever period is the shorter. A 10-day course of penicillin may be given to eradicate any streptococcal infection. Prophylaxis of streptococcal infection in patients who have had rheumatic fever is dealt with on p. 56.

DRUG TREATMENT OF RHEUMATOID ARTHRITIS

Best results are obtained with early hospital treatment, rest, physiotherapy and drugs.

The principles of drug therapy are as follows:—

Relief of Pain

Aspirin (2 to 6 G. a day) is the drug of choice, with phenylbutazone in exceptional cases, for only a minority of patients can tolerate phenylbutazone over very long periods. Paracetamol is sometimes useful, but it is rather less effective than Codeine Compound Tablets. It may be used in patients intolerant of aspirin.

Suppression of Local Inflammatory Process

Systemic Adrenocortical Steroids. Steroids are in no way curative in this disease. Their effects are only temporary and administration must continue indefinitely if relief is to be maintained. Some patients become refractory to steroids, and the disease may also progress even in the presence of symptomatic relief. Chronic use also exposes the patient to the side-effects of the steroids which can be very troublesome. In addition patients' own adrenal cortices atrophy as a result of the administration and so they are exposed to the risks of adrenal insufficiency if requirements suddenly increase, as in infections, or if they should stop taking the hormone. Steroids are not a substitute for other treatments and should only be used when these others have failed. Patients must be mentally stable and co-operative and prepared to accept partial improvement, if this is all that can be obtained without inducing side-effects, as it well may be. Those who have had the disease for more than two years are liable, once steroids have been started, to need them indefinitely, so that the risk of side-effects is substantial. It is also necessary to consider carefully the contra-indications to the use of steroids, p. 94. Steroids will not help patients whose disability is due to irreversible joint damage. There is evidence that prednisolone is superior in therapeutic effect to cortisone and to aspirin (9) and that the dose should not exceed 10 mg. a day over long periods. The decision to use a steroid in rheumatoid arthritis should only be taken by an expert.

Intra-articular Injection of Hydrocortisone or Prednisolone may be used when one joint is relatively more severely affected than others or when there are contra-indications to systemic therapy, such as pregnancy, diabetes or tuberculosis. Benefit from one injection seldom lasts more than two weeks. Skill and care are required for successful therapy. Aseptic precautions must be extreme, for the steroid will suppress inflammatory response and any introduced infection may spread dramatically. An antibiotic (e.g. neomycin) is often incorporated in the steroid solution to help prevent infection. Doses of 125 mg. hydrocortisone in a large joint may be used, small joints such as the fingers receiving 10 to 20 mg.

Arrest of the Rheumatoid Process

The value of gold for this purpose is still debated (see below); chloroquine or hydrochloroquine (200 to 300 mg. base a day) or other antimalarials seem to exert a favourable influence in some cases but treatment must be prolonged. Chloroquine is also used in other collagen diseases. High doses occasionally cause corneal opacities, damage to the retina and bleaching of the hair.

Gold

Gold salts were first used in rheumatoid arthritis in 1929 in the mistaken belief that the arthritis was a tuberculous manifestation. Opinions on the therapeutic merit of gold have fluctuated, but there has never been any doubt about its dangers, which can be serious. Gold is said to be the most effective agent for preventing progression of the arthritis, best results being obtained in early cases. The decision to employ gold should only be undertaken by physicians with special experience of the disease. Sodium Aurothiomalate Injection, B.P., is given i.m. weekly, 10 mg. for two weeks, 20 mg. for two weeks and then 50 mg. weekly until one gram has been given, after which 50 mg. may be given monthly. This can be continued indefinitely, in the absence of toxicity, until the disease becomes inactive. Toxic effects occur in about 30% of cases, pruritus, dermatitis, glossitis and stomatitis which may ulcerate, most commonly, and also blood dyscrasias, hepatic and renal damage, peripheral neuritis and encephalopathy all occur. The patient should be warned to report any untoward symptoms at once. Serious effects are rare if the patient is carefully observed and the drug stopped at the earliest sign of toxicity. The urine should be examined for albumen before each injection. Gold should be stopped at once on the appearance of any toxic effect and should not be given again unless the reaction was trivial, in which case it may be recommended at lower dose after the toxic effect has disappeared but not before six weeks have passed. Great caution must always be exercised. Toxic effects are most common early in the course of treatment but may occur at any time. Any serious toxic effect, or one which does not subside rapidly, should be treated with dimercaprol, p. 431. Adrenocortical steroids may be useful as at least some of the toxicity is due to hypersensitivity. The mode of beneficial action of gold, if any, in rheumatoid arthritis is unknown.

Some physicians do not use gold because they consider it ineffective as well as dangerous. Its true place, if any, will only be decided when properly designed clinical trials have been done. The fact that there is still room for debate on the elementary question whether gold does or does not have any beneficial action in rheumatoid arthritis is a reproach to modern medical practice.

Ankylosing Spondylitis

Aspirin and allied drugs may be used for pain and phenylbutazone is especially effective. Adrenocortical steroids are not very helpful and radiotherapy would be preferred in severe cases more often if it were not for the risk of leukæmia from the heavy doses necessary. Physical methods of treatment are of the first importance to prevent deformity.

Osteoarthritis

Aspirin and phenylbutazone give most symptomatic relief. Severely affected large joints, especially when acutely exacerbated by trauma, benefit from intra-articular hydrocortisone.

DRUGS USED IN GOUT

The principal drugs used in gout may be listed:—

Drug	*Principal mechanism of effect*
colchicine and demecolcine	analgesic and anti-inflammatory
phenylbutazone	analgesic, anti-inflammatory and uricosuric
salicylates	analgesic and uricosuric (p. 168)
probenecid	uricosuric
adrenocortical steroids & corticotrophin	anti-inflammatory and uricosuric

Colchicine and Demecolcine

These are alkaloids from the autumn crocus. They are antimitotic agents of little use in neoplastic disease, but valuable in gout in which they relieve the pain and inflammation in a few hours. Such rapid relief is considered to confirm the diagnosis, though failure does not prove the patient has not gout. The mechanism of action is unknown, and colchicine does not increase uric acid excretion. Colchicine is useless in pain or arthritis which is not due to gout.

Colchicine is absorbed from the alimentary tract; its fate in man is unknown, but in animals it is excreted into the intestine.

Effects of overdose may be severe. Gastro-enteritis occurs with abdominal pain, vomiting and diarrhœa which may be bloody after both oral and i.v. administration. Renal damage can occur and, rarely, blood dyscrasias.

In acute gout colchicine, 1 mg. orally may be given, followed by 0·5 mg. 2-hourly until either relief or toxic effects occur. Benefit is usually felt in two to three hours and is marked within 12 hours. 4 to 8 mg. are usually needed, but colchicine, like all drugs, sometimes fails. If gastro-intestinal side-effects are severe the patient may tolerate demecolcine, the dose of which is the same. The results of colchicine therapy are best if the drug is given early in an attack.

It is now known that colchicine is an effective suppressant prophylactic against gout in doses of 0·5 to 1 mg. a day, or on alternate days.

Cinchophen and Neocinchophen

These are uricosuric agents which are obsolete because of the high incidence of serious and sometimes fatal liver damage. Otherwise they resemble salicylates.

Probenecid (Benemid)

Probenecid is a uricosuric agent. It was discovered as a result of a search for agents that would prevent penicillin excretion by the renal tubule and so enable high penicillin blood levels to be maintained by small doses. Probenecid does this effectively, but as penicillin has become so cheap there is no longer any particular advantage in not adopting the alternative and simply increasing the dose. Probenecid is however occasionally used in infections where exceptionally high penicillin blood levels are desired, as in some cases of subacute bacterial endocarditis, and in children in whom large and frequent injections are undesirable.

Probenecid, because it interferes with renal tubular excretion of penicillin (and PAS as well as other substances) and reabsorption of uric acid, is clearly interfering with a renal tubular transport process, probably by competition. It does not affect the excretion of other antibiotics.

Probenecid is well absorbed from the alimentary tract, passes across the glomerulus and is reabsorbed by the renal tubule. It is metabolised slowly and the metabolites are lost in the urine. It causes gastro-intestinal upset in a few patients and hypersensitivity effects occasionally.

The important use of probenecid is in gout, for it is a most effective uricosuric agent. It has no analgesic effect. To prevent gout it is given orally, 0·5 G. or occasionally 1 G., twice a day. The blood uric acid level falls rapidly at first and then levels off at about two-thirds of the initial level. Crystals of urate may appear in the urine and some advise that the urine should be made alkaline (with potassium citrate or sodium bicarbonate) for the first month of probenecid (or any other uricosuric) administration to avoid the dangers of mechanical obstruction. Care should be exercised if this is done because some gouty patients have renal insufficiency.

Unfortunately the desired effect of probenecid only occurs at high plasma levels of the drug. Low blood levels may actually induce retention of uric acid, the very reverse of what is desired. Rarely an attack of gout occurs at the beginning of probenecid therapy and this has been attributed to the drug, perhaps unjustly. It can obviously create an unfavourable impression if the patient has simply been told the drug will prevent his gout.

The therapeutic effects to be anticipated are reduction in frequency of attacks of gout, prevention of the formation of new, and reduction in the size of existing, tophi.

Zoxazolamine

Zoxazolamine, ordinarily used as a centrally acting muscle relaxant, happens to be also an effective uricosuric. It can probably be used as a probenecid substitute (125 mg. three times a day).

Sulfinpyrazone (Anturan) is another uricosuric.

DRUG TREATMENT OF GOUT

Acute Gout. Both colchicine and phenylbutazone are highly effective in acute gout, terminating the attack in a few hours. Colchicine is usually tried first and phenylbutazone used if colchicine is unsatisfactory. Administration of colchicine is described on p. 179. Phenylbutazone can be used thus, a loading dose of 600 mg. orally is followed by two doses of 200 mg. 2-hourly and then 100 mg. three or four times a day. Improvement usually begins in a few hours and recovery is usually complete in one to four days, but may take up to two weeks. If gastric symptoms occur phenylbutazone may be given i.m. (600 to 1,000 mg. daily at first).

Phenylbutazone and colchicine can be used together and relief may be quicker than with either alone, but it is suggested that this should only be done if experience shows that the response to both drugs used singly is unsatisfactory, for both are toxic.

If these drugs fail adrenocortical steroids or corticotrophin may be used. Relapse may follow withdrawal.

Recurrent Gout may be prevented by probenecid. For doses see p. 179. Salicylates are not satisfactory as uricosuric agents, but can be used. They must not be given concurrently with probenecid as they interfere with its action.

Impaired renal function, provided it is mild, does not contra-indicate probenecid.

Colchicine also prevents gout, probably by suppressing acute attacks at their inception. It has no effect on urate excretion. Not surprisingly a combination of probenecid and colchicine has been found to give good results, the true prophylactic effect of probenecid being combined with the suppressant anti-inflammatory action of colchicine.

After two years free from attacks the probenecid dosage may be reduced or omitted and the patient may take only a little colchicine. The best régime for each patient must be found by experiment. The utility of zoxazolamine is as yet undecided.

Vigorous diuretic therapy can precipitate an attack of gout.

Chronic Tophaceous Gout. Tophi can sometimes be reduced in size and even removed by the use of uricosuric agents such as probenecid.

GUIDE TO FURTHER READING

On Pain and Analgesics

(*1*) BEECHER, H. K. (1957). Measurement of pain. *Pharmacol. Rev.*, **9**, 59.

(*2*) BEECHER, H. K. (1956). Relationship of significance of wound to pain experienced. *J. Amer. med. Ass.*, **161**, 1609.

(*3*) BEECHER, H. K. (1956). The subjective response and reaction to sensation. *Amer. J. Med.*, **20**, 107.

(*4*) DENTON, J. E., and BEECHER, H. K. (1949). Methods in the clinical evaluation of new analgesics. *J. Amer. med. Ass.*, **141**, 1051.

(5) HEWER, A. J. H., *et al.* (1949). A clinical method of assessing analgesics. *Lancet*, (*i*), 431.

(*6*) FRIEDMAN, A. P., and MERRITT, H. H. (1957). Treatment of headache. *J. Amer. med. Ass.*, **163**, 1111.

(7) KEELE, C. A. (1959). Measurement of analgesia. *In* Quantitative Methods in Human Pharmacology and Therapeutics. Ed. D. R. LAURENCE. London: Pergamon Press.

(*8*) KUNKLE, E. C., and WOLFF, H. G. (1951). Headache. *In* Modern Trends in Neurology. 1st series. Ed. A. FEILING. London: Butterworth.

(*9*) MODELL, W., and HOUDE, R. W. (1958). Factors influencing clinical evaluation of drugs with special reference to the double-blind technique. *J. Amer. med. Ass.*, **167**, 2190.

(*10*) BEECHER, H. K. (1960). Control of suffering in severe trauma. *J. Amer. med. Ass.*, **173**, 534.

On Opiate Analgesics

(*1*) The history of heroin and other articles. *Bull. Narcot.*, 1953, **5**, part 2.

(*2*) The controversy over the proposal to ban heroin in Britain may be followed in:—

Brit. med. J., 1955, (*i*), 1264.
Brit. med. J., 1955, (*ii*), 1319, 1375, 1437, 1453, 1507, 1626.
Brit. med. J., 1956, (*i*), 298.
Lancet, 1955, (*i*), 1277, 1311.

(*3*) Maurer, D. W., and Vogel, V. H. (1954). Narcotics and Narcotic Addiction. Springfield: Thomas.

(*4*) Woods, L. A. (1956). The pharmacology of nalorphine. *Pharmacol. Rev.*, **8**, 175.

(5) Curreri, A. R., and Gale, J. W. (1950). Effect of analgesics and antispasmodics on common duct pressures. *Ann. Surg.*, **132**, 348.

On Non-narcotic Analgesics

(*1*) Editorial (1959). Aspirin plain and buffered. *Brit. med. J.*, (*i*), 349.

(*2*) Hart, F. D., and Burley, D. (1959). Phenylbutazone and its derivatives. *Brit. med. J.*, (*i*), 1087.

(*3*) Muir, A., and Cossar, I. A. (1959). Aspirin and gastric hæmorrhage. *Lancet*, (*i*), 539.

(*4*) Stubbé, L. Th. F. L. (1958). Occult blood in the fæces after administration of aspirin. *Brit. med. J.*, (*ii*), 1062.

(5) Segar, W. E., and Holliday, M. A. (1958). Physiologic abnormalities of salicylate intoxication. *New Engl. J. Med.*, **259**, 1191.

(*6*) Illingworth, R. S., *et al.* (1957). Acute rheumatic fever in children. A comparison of six forms of treatment in 200 cases. *Lancet*, (*ii*), 653.

(*7*) Talbott, J. H., and Lockie, M. L. (1958) (Editors). Progress in Arthritis. New York: Grune and Stratton.

(*8*) Rheumatism and arthritis: review of American and English literature of recent years. *Ann. intern. Med.*, 1959, **50**, 366 and 633.

(*9*) Medical Research Council (1959). Comparison of prednisolone with aspirin and other analgesics in the treatment of rheumatoid arthritis. *Ann. Rheum. Dis.*, **18**, 173.

(*10*) Baragar, F. D., and Duthie, J. J. R. (1960). Importance of aspirin as a cause of anæmia and peptic ulcer in rheumatoid arthritis. *Brit. med. J.*, (*i*), 1106.

Chapter 9

DRUG ADDICTION, TOBACCO, ALCOHOL

DRUG ADDICTION AND DRUG HABIT

"ALL the naturally occurring sedatives, narcotics, euphorics, hallucinogens, and excitants were discovered thousands of years ago, before the dawn of civilisation. . . . By the late Stone Age man was systematically poisoning himself. The presence of poppy heads in the kitchen middens of the Swiss Lake Dwellers show how early in his history man discovered the techniques of self-transcendence through drugs. There were dope addicts long before there were farmers."*

The drives that persuade or compel a person more or less mentally normal to resort to drugs to obtain "chemical vacations from intolerable selfhood" (*1*) will not be considered here, but some account of the pharmacological aspects of addiction is appropriate. "That humanity at large will ever be able to dispense with Artificial Paradises seems very unlikely. Most men and women lead lives at the worst so painful, at the best so monotonous, poor and limited that the urge to escape, the longing to transcend themselves if only for a few moments, is and has always been one of the principal appetites of the soul" (*1*). The dividing-line between occasional use of drugs for this purpose and their abuse is not easily drawn. "Normal" people seem to be able to use alcohol for their occasional purposes without harm but, given the appropriate degree of mental abnormality and environmental adversity, man may become addicted.

Drug addiction may be defined as "a state in which a person has lost the power of self-control with reference to a drug, and abuses the drug to such an extent that the person or society is harmed" (*2*). It is characterised by compulsive and repeated use of a drug, the harm resulting from which varies with the degree of abnormality of the addict. Also one or more of the following phenomena occur:—

1. Tolerance.
2. Physical dependence, which means that there is physical illness if the drug is withheld (abstinence or withdrawal syndrome).
3. Emotional dependence.

It has been pointed out that "anyone tempted to rely upon a very narrow or arbitrary definition of addiction should remember that, in a very strict sense food produces not only tolerance, but emotional dependence and physical dependence as well" (*2*).

---

* HUXLEY, A. (1957). *Ann. N.Y. Acad. Sci.* 67, 677.

The difference between drug habit and drug addiction has also proved difficult to define. Such a distinction is useful, for it seems a little inappropriate to class the millions who habitually lean on tobacco and alcohol to make life more worth living with the person disabled socially by heroin addiction. But perhaps they are merely stages in the same process, for drug habit and drug addiction certainly merge into one another. Nor is drug addiction necessarily disabling; many morphine addicts, given adequate supplies, can carry on an outwardly normal life.

The World Health Organisation has tried to draw a distinction between addiction and habituation*:—

Drug Addiction is a state of periodic or chronic intoxication produced by the repeated consumption of a drug. Its characteristics include:—	**Drug Habituation** is a condition resulting from the repeated administration of a drug. Its characteristics include:—
1. An overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means.	1. A desire (but not a compulsion) to continue taking the drug for the sense of well-being that it engenders.
2. A tendency to increase the dose.	2. Little or no tendency to increase the dose.
3. A psychological and generally a physical dependence on the effects of the drug.	3. Some degree of psychic dependence on the effect of the drug, but absence of physical dependence and hence of an abstinence syndrome.
4. An effect detrimental to the individual and to society.	4. A detrimental effect, if any, primarily to the individual.

The statement that a drug addict has a compulsion to obtain a drug "by any means" has been justly criticised as altogether too strong (*2*). Serious crime is seldom the result of such compulsion, although petty crime to obtain money for drugs is common enough in places where addiction is common.

The mechanisms of physical dependence on drugs and development of tolerance are ill understood but various theories have been proposed (*3*). There is commonly cross-tolerance between drugs of similar, and sometimes even of dissimilar, chemical groups, *e.g.* barbiturates and alcohol.

Physical dependence develops with cerebral depressants, but is less or absent with stimulant drugs. Cocaine and marihuana, though drugs of addiction, induce no physical dependence and amphetamine probably does not. But even so, probably the most important single distinction between addiction and habituation is that of physical dependence. A drug habit can be suddenly broken without the subject becoming physically ill, whereas a true addict ordinarily experiences a physical illness on sudden withdrawal of the drug. Even this distinction is not always clear, for the mental misery of the deprived habitual tobacco smoker may manifest itself in physical symptoms, digestive disturbance and tremors.

---

* Eddy, N. B. (1957). *J. Amer. med. Ass.*, 163, 1622.

Habituation occurs to a wide range of drugs, including aspirin, bromides, barbiturates, tobacco, tea, coffee, alcohol and probably to some of the new tranquillisers, some of which are also drugs of addiction.

Although "no drug possesses mysterious powers to subjugate a human being" (*2*), there is danger in experimenting with the more potent agents. It is said that a feeling of pleasure at the first experience of a drug is an index of "addiction proneness", and this was evidently so for that famous addict, Thomas de Quincey, who, in 1804, suffering from facial pain, "met a college acquaintance who recommended opium". He purchased some tincture and went home. " . . . I took it; and in an hour, O heavens! what a revulsion! what a resurrection, from its lowest depths, of the inner spirit! . . . .That my pains had vanished, was now a trifle in my eyes; this negative effect was swallowed up in the immensity of those positive effects which had opened before me, in the abyss of divine enjoyment thus suddenly revealed. Here was a panacea . . . for all human woes; here was the secret of happiness, about which philosophers had disputed for so many ages, at once discovered; happiness might now be bought for a penny, and carried in the waistcoat-pocket; portable ecstasies might be had corked up in a pint-bottle; and peace of mind could be sent down by the mail" (*4*). Or, as a modern American addict has more succinctly put it, "They all think they can take just one joy-pop but its the first one that hooks you" (*2*).

On the other hand many people experience nothing but unpleasantness with the opium group of drugs. In case these quotations should give an impression that there is anything amusing or romantic about drug addiction, it may be categorically stated that drug addiction is, in virtually all cases, a ruinous, degrading and sordid state not only for the addict, who is a psychopath, but for his relations and friends. The opinion of de Quincey is unsound, and his career as an addict was quite exceptional.

Despite the fact that the sale of opium to the public in Britain was not restricted by law until 1923 there was never a large body of opium addicts in the country. Restriction was inevitable, however, because of the ease with which morphine can be extracted from it, a standing temptation to unscrupulous people who in some countries promote addiction, especially among juveniles, for their own profit. The argument of Thomas de Quincey in 1821, "what a man may lawfully seek in wine, surely he may lawfully find in opium" does not now arouse our sympathy. Nor are we as surprised as he was that fourteen insurance offices in succession "repulsed me as a candidate . . . on that solitary ground of having owned myself to be an opium-eater" (*4*).

It would be unprofitable to attempt to list all the drugs to which addiction can occur, for it is probably true that any drug that alters consciousness can cause addiction. Habituation does not require that a drug should have psychic effects, the habitué's beliefs as to what it does are as important.

Since the 19th century, addiction to chloral and paraldehyde have occurred as well as addiction to alcohol and opium. Now pleasanter synthetic drugs have taken their place. Ether addiction is not very rare and anæsthetists have acquired habits for a wide variety of agents including nitrous oxide, cyclopropane and halothane. In Britain, doctors, dentists and nurses form a substantial proportion of the small number of known addicts to opiate drugs; it may be hoped that this is because of easier access rather than because of a disproportionate incidence of personality disorder amongst them. The problem of addiction to barbiturates and other hypnotics, often unrecognised, grows as that of opiate addiction diminishes.

The treatment of drug addiction consists in withdrawal of the drug, perhaps the least important facet of therapy, followed by attempts at social rehabilitation, the most important aspect. In the case of drugs which cause physical dependence, withdrawal may be gradual (over about 10 days), or sudden, provided that in the latter case steps are taken to control the abstinence syndrome. This may be done by judicious use of alternative drugs of similar kind, for instance a heroin addict can be given methadone; an alcoholic may be given paraldehyde; or alternatively a combination of a barbiturate and chlorpromazine may be effective. If a patient is in very poor physical condition withdrawal should be postponed until he is better.

Relapsed addicts who live a fairly normal life are sometimes best treated by supplying drugs under supervision. There is no legal objection to doing this in Britain, but naturally this course, which abandons hope of cure, should not be adopted until it is certain that cure is virtually impossible. The doctor who undertakes such supply may find that he soon attracts the interest of the Home Office.

Prevention of Drug Addiction Arising Out of Medical Use of Drugs

It is probable that many addicts who claim that their state is the result of misuse of drugs by their medical attendants are not speaking the truth, but trying to shift a feeling of guilt to other shoulders.

The risk of making a normal person addicted to narcotic analgesics during therapeutic use is small if drugs are handled properly, but it exists in chronic recurrent painful conditions. It is wise to withhold drugs of addiction from such people as long as possible and then, if they must be used, to space the doses as widely as possible. It may also sometimes be wise to conceal the nature of the drug, especially if the patient is mentally abnormal or unstable.

In patients who have only a brief expectation of life the production of addiction is of little or no importance and need not generally be taken into consideration when planning therapy.

TOBACCO

Tobacco was introduced to Europe from South America in the 16th century. For some time smoking attracted a good deal of opprobrium and was forbidden by both Church and State, but this did not stop it and soon the State found that tobacco was a habit-forming drug of sufficient power to bear heavy taxation without causing habitués to abandon it, and yet of insufficient power to cause dangerous disruption of the community. This applies to alcohol as well, and it has been pointed out that "So excellently habit-forming are they in fact, from the Government's point of view, that they can now be made to pay for the whole of the National Health Service, including its vast hospital services and for all the other free untaxed tranquillisers prescribed by doctors",* and a substantial sum is still left over.

The pharmacological effects of tobacco are primarily those of nicotine. Nicotine stimulates the cholinergic endings of nerves whose cell bodies lie in the central nervous system, *i.e.* it acts at autonomic ganglia and at the neuromuscular junction. This is what is meant by the term "nicotine-like" or "nicotinic" effect. Higher doses paralyse at the same points.

In addition nicotine stimulates the central nervous system, including the vomiting centre, both directly and via the carotid sinus; tremors and convulsions may occur. As with the peripheral actions, depression follows stimulation. Nicotine causes release of the antidiuretic hormone of the posterior pituitary gland and has been used in a test for diabetes insipidus. The "sedative" or calming effect of smoking remains unexplained. Thus the actual effects experienced by the smoker taking his first steps in the art (*9*) are complicated and only partly predictable, but are often unpleasant.

The effects of chronic indulgence in tobacco on the mind have not been elucidated. How far the pleasurable effects of tobacco smoking (or chewing or snuffing) are due to pharmacological action of nicotine on the brain is unknown. It is disputable whether a true addiction to nicotine occurs. There is no doubt that the psychological aspects of indulgence play a large part; the ritual of "lighting up", the first rather deep inhalation to get started (some habitual smokers, especially pipe smokers, never inhale to a significant extent), the offering or accepting of tobacco are important. "The psychiatrists have made their characteristic contribution to the problem. 'Getting something orally', one asserts . . . 'is the first great libidinous experience in life'; first the breast, then the bottle, then the comforter, then food and finally the cigarette" (*1*).

---

* Sargant, W. (1956). *Brit. med. J.*, (*i*), 939.

The demonstrable deleterious effects of heavy tobacco smoking are quite enough without there being any necessity for those who disapprove of the habit to invent others as has been done in the past.

There is good evidence of an association between smoking and bronchitis, peptic ulcer and bronchial carcinoma. An association does not, of course, prove causation, but when an association is close it may sometimes be wiser to assume causation pending the collection of final evidence on the point than to await the final proof before taking any action. Symptoms of peripheral vascular disease may be made worse by heavy smoking and it also causes amblyopia.

Whether a patient should give up smoking depends on numerous factors including the amount of evidence that smoking causes his disease, the evidence whether smoking aggravates the disease in people in general and in the patient in particular, and the patient's attitude to his habit. Some people are so miserable without tobacco that the risk of exacerbation of disease is the lesser evil. To smoke, or not to smoke, is not primarily a problem of pharmacology.

For further discussion of the effects of tobacco the articles in the list on p. 198 may be read as a start.

ETHYL ALCOHOL

Although the importance of alcohol in therapeutics is small its sociological significance is so immense that a fuller account of its pharmacology is warranted than would otherwise be appropriate.

The history of alcohol is part of the history of civilisation "ever since Noah made his epoch-making discovery".* Perhaps its main use in therapeutics has been with opium as an analgesic and surgical anæsthetic before the introduction of ether.

Alcohol acts on the central nervous system in the manner of the inhalation anæsthetics.

Absorption of alcohol taken orally is rapid, some from the stomach, but most from the small intestine. With moderate amounts the highest blood levels, as might be expected, are reached with stronger solutions.

However, very strong solutions are absorbed relatively slowly because high concentrations of alcohol inhibit gastric peristalsis and so delay the arrival of the alcohol in the small intestine. Large doses taken in very dilute solution are absorbed relatively slowly because of the large amount of water.

* *Genesis*, 9, 21; Huxley, A. (1957). *Ann. N.Y. Acad. Sci.*, **67**, 675.

Absorption is delayed by food, especially milk, whose effect is probably due to the fat it contains. But this is not simply an effect of any fat, for suet and olive oil are less effective. Carbohydrate also delays absorption of alcohol and so alcohol in beer is absorbed more slowly than a simple solution. There is evidence that habitual drinkers absorb alcohol more rapidly than others, but they excrete and metabolise it at normal rates.

After absorption alcohol rapidly diffuses throughout the body water and is not selectively stored in any tissue. If food is taken simultaneously alcohol disappears from the blood more rapidly than otherwise; it is not known how this happens.

Maximum blood levels after oral alcohol therefore depend on numerous factors including the total dose, the strength of the solution, the time over which it is taken, the presence or absence of food, the time relations of taking food and alcohol and the kind of food eaten, as well as on the speed of metabolism and excretion. A single dose of alcohol, say 60 ml. (equivalent to 145 ml. whisky, five to six "whiskies", or three pints, 1,700 ml. of beer) taken over a few minutes on an empty stomach will probably produce maximal blood concentration at from one to one-and-a-half hours and will not all be disposed of for six to eight hours. There are very great individual variations. About 90% of absorbed alcohol is metabolised, the remainder being excreted in the breath, the urine and the sweat; convenient methods of estimation of alcohol in all these are available. The rate at which alcohol is metabolised varies little with the concentration in the body, it is constant at about 10 to 15 ml. per hour and is uninfluenced by the development of tolerance.

Alcohol is chiefly metabolised by enzyme systems in the liver, first into acetaldehyde and then to acetate which is metabolised to carbon dioxide and water. Some chemicals, for instance disulfiram (Antabuse), block the conversion of acetaldehyde to acetate so that the acetaldehyde accumulates and makes the subject feel ill (p. 194).

The most important effects of alcohol are on the central nervous system in which it depresses the higher centres first, then the lower, like other anæsthetic agents. It is not a stimulant, hyperactivity, when it occurs, being due to removal of inhibitory effects exercised by higher centres. With increasing doses the subject passes through all the stages of general anæsthesia and may die of respiratory depression. Psychic effects are the most socially important, and it is to obtain these that the drug is habitually used in so many societies, to make social intercourse not merely easy but pleasant. They have been admirably described by Sollmann: "The first functions to be lost are the finer grades of judgment, reflection, observation and attention—the faculties largely acquired through education, which constitute the elements of the restraint and prudence that man usually imposes on his actions. The orator allows himself to be carried by the impulse of the moment, without reflecting on ultimate consequences, and as his expressions become freer, they acquire an appearance of warmth, of feeling, of inspiration. Not a little of this inspiration is contributed by the audience if they are in a similar condition of increased appreciation. . . . Another characteristic feature, evidently resulting from paralysis of the higher functions, is the loss of power to control moods."* Environment, personality, mood and dose of alcohol are all relevant to the final effect.†

There is now every reason to believe that, in general, efficiency, both mental and physical, is reduced by alcohol in any amounts, however small. There is an important exception; the person who is so disabled by anxiety or nervous tension that his performance is gravely impaired may improve with alcohol. The alleviation of great anxiety may improve performance more than the alcohol depresses it. Such people, mentally abnormal, are more liable to become alcohol addicts. Another exception is a minority of introverted people; it is referred to below.

Innumerable tests of physical and mental performance have been used to demonstrate the effects of alcohol. Results show that alcohol reduces visual acuity and delays recovery from visual dazzle, it impairs taste, smell and hearing, muscular co-ordination and steadiness and prolongs reaction time. It also causes nystagmus and vertigo. At the same time the subjects commonly have an increased confidence in their ability to perform well when tested, even after quite low doses, evidently a very undesirable effect when the subject is in a position where failure to perform well may cause an accident, as in driving a car.

The effects of alcohol on motor driving have been the subject of a great deal of well-deserved attention and many countries have made laws designed to prevent motor accidents caused by alcohol. The problem has nowhere been solved. In general it can be said that the weight of evidence points to a steady deterioration of driving skill and an increased liability to accidents which begins with the entry of the smallest amounts of alcohol into the blood and steadily increases with blood level.

Unfortunately it is not possible to observe and make measurements of driving skill in subjects who are both unaware that they are under observation and who are yet driving under normal traffic conditions. The undoubted tendency of alcohol to increase distractibility, proneness to take risks and carelessness has not therefore been measured under normal conditions; in experimental conditions the well-known ability of an alcoholic to "pull himself together" and to perform well temporarily when he knows he is being tested will tend to give an unduly favourable picture of the effects of alcohol, but despite this the evidence for its evil effects is impressive.

---

* SOLLMANN, T. (1957). Manual of Pharmacology, 8th ed. Philadelphia; Saunders.

† "That which hath made them drunk hath made me bold." Lady Macbeth in *Macbeth*, Act 2, Scene 2. W. SHAKESPEARE.

In one study on Manchester bus drivers, all of whom were recipients of awards for safe driving, it was found that even with these experienced professionals there was no "safe" blood-alcohol level below which it was certain that no impairment of judgment would occur.

The drivers were invited to estimate through what gaps they *thought* they could drive their bus, were then given a driving test to determine the smallest gap through which they would *actually attempt* to drive and finally were told to drive through gaps regardless of their opinions. The main conclusion was that "the performance of the drivers deteriorated, they were involved in greater hazards, and they displayed a false confidence in their driving ability" (*5*).

In another study using a motor driving trainer it was found that alcohol even in small doses caused drivers to move away from the kerb and to tolerate steering swings towards the road centre but not towards the kerb, also steering wheel movement increased and its timing became more faulty. An attempt to correlate these responses with personality suggested that extraverts were not worried by the stress imposed by taking alcohol, they did not alter their speed greatly but were much less accurate. Introverts however appeared to try to compensate for the alcohol effect, earnestly striving to show that they were efficient, with the result that they over-reacted to the situation, moving the steering wheel more and changing speed, some slowing right down and others seemingly trying to show how quickly they could drive. In the introvert group 2 out of 9 subjects made fewer errors. No extravert made fewer errors (*6*).

There can be little doubt that alcohol plays a huge part in causing motor accidents, being a factor perhaps in as many as 50%. The official police figures are small and bear no relation to reality, for a charge can only be brought against an individual who can be proved to be "drunk" to the extent of showing abnormal behaviour or inco-ordination; lesser degrees of alcoholism are too hard to prove. This is why, in some countries, great stress is laid on blood alcohol levels; these are likely to be more widely employed as the serious impairment of judgment caused by even small amounts of alcohol is recognised and the consequences condemned by society. Schemes for examining subjects for "intoxication" usually consist of general observations on behaviour and simple tests for physical inco-ordination. But the carelessness which follows taking even very small amounts of alcohol and which is probably a far commoner cause of accidents than is physical inco-ordination cannot be shown by any tests that can reasonably be applied, for such people can easily "pull themselves together" when they realise that they are being examined it is very dangerous to attempt to control him with barbiturates or opiates because of the risk of inducing severe respiratory depression as a result of synergism of the drugs. In patients who are comatose the stomach may be emptied by tube, emesis being dangerous in any patient with impaired consciousness. Respiratory stimulants (nikethamide) are used as required; circulatory failure may occur. The danger of inhaling vomit is great once the victim is in coma. Claims have been made that both pyridoxine (100 mg. i.v.) and fructose (1·5 G./Kg. orally, a generally accessible source is honey in which about half the sugar is fructose,* or by slow i.v. infusion) reduce blood alcohol levels and are valuable in acute intoxication. These claims have not been conclusively substantiated.

Chronic Alcoholism (alcohol addiction) is liable to cause a variety of psychotic states and, after many years, nutritional deficiencies. The latter are due to the fact that alcoholics suffer from loss of appetite with chronic gastritis, may be taking nearly all the calories they need as alcohol and may have no money to spend on food. "Alcoholic" hepatic cirrhosis is not due solely to the effects of alcohol on the liver cells.

The end-stage, of dementia with memory loss, deterioration in social habits, slurred speech and gait and "blackouts", which may be epileptic, is typical. More florid chronic psychotic conditions with delusions and hallucinations are probably the result of abnormal previous personality rather than any intrinsic effect of alcohol on the nervous system.

Sudden withdrawal of alcohol, which may occur when an ill or injured alcoholic is admitted to hospital, may precipitate an acute psychotic attack. Psychiatry and sedatives may be required. It is usual to administer vitamins, especially aneurine, of which alcoholics are commonly deficient. Corticotrophin and cortisone may be useful if there is severe collapse. The general subject of drug addiction is discussed on p. 183.

In alcoholics who are fairly well and co-operative an attempt may be made to discourage drinking by the use of disulfiram. This blocks the metabolism of alcohol at the stage where acetaldehyde is formed. The accumulation of this substance in the blood is so unpleasant that the patient does not wish to experience it again; disulfiram thus reinforces his perhaps otherwise ineffective will power. Such therapy by intimidation, whether self-administered or thrust on the patient, is not to be expected to play an important part in the treatment of alcoholism, a disease which is primarily a manifestation of psychological disorder. When a patient is given disulfiram it is important to give a test dose of alcohol under supervision, so that he can be taught what to expect and also to induce in him an aversion from alcohol. That this is not a treatment to be lightly undertaken is shown by the fact that, though rare, deaths have occurred following the "test drink". A typical reaction of medium severity comes on about five minutes after taking alcohol and consists of generalised vasodilatation and fall in blood pressure, sweating, dyspnœa, headache, chest pain, nausea and vomiting. Severe reactions include convulsions and circulatory collapse.

---

* Sucrose is hydrolysed to dextrose and fructose in the intestine, but this takes time.

It is clear that no patient should be given disulfiram without the fullest previous explanation and the certainty that he understands the possible serious consequences of drinking a lot of alcohol in a few minutes.

The disulfiram-alcohol interaction has long been known to workers in the rubber industry in which the substance is used, but it was not applied to therapeutics until after the chance experience of two Danish pharmacologists. "Dr. Hald suggested that disulfiram could be employed as an anthelminthic because it had a very strong fixation to copper ions. It was probable that some enzymes of the oxidation system of intestinal worms were copper containing, and copper-containing enzymes are unknown in. . . higher animals, including man." The drug was tested on rabbits infected with worms and results were sufficiently encouraging to warrant clinical trial.

"According to the custom in this house we never give a new drug to patients before we have taken at least double the recommended dose ourselves. During this routine procedure Dr. Hald and I discovered that we had developed a hypersensitivity to alcohol. We compared symptoms and found them identical. The only thing we had in common was the tablets. A test on a third person in our laboratory confirmed the observation."*

Further investigation disclosed the mechanism of the effect. Other drugs are used in the "aversion" treatment of alcohol addition; they are mostly emetics.

Alcoholic Drinks

The pharmacology of alcoholic drinks is not the same as the pharmacology of alcohol. The drinks contain other ingredients which may reduce the rate of absorption of alcohol (carbohydrate in beer), act as a carminative (essential oils), or diuretics (juniper oil in gin). It is certainly widely believed that the toxicity of all varieties of alcoholic drinks is not solely dependent on their alcoholic content and that ill-effects are likely to be more severe if several varieties are taken within a short time; this is expressed as advice "not to mix your drinks". There is no conclusive evidence on this point, but what there is does not support the popular belief that toxicity of drinks differs from that of ethyl alcohol. The content of higher alcohols (fusel oil) to which the ill-effects are often attributed is very small and in any case they are hardly more toxic than ethanol. It should be remembered that when enough alcoholic drink has been taken to cause "hangover" the subject has commonly debauched himself in other ways too, with tobacco, food, polluted atmosphere and fatigue, and in addition is expecting to feel ill the next day.

---

* Dr. Erik Jacobsen. Personal communication.

Since there are many more important subjects for research, the final elucidation of this point in the near future is unlikely, and indeed very strong evidence would be needed to shake, although not to confirm, the faith of most people that this or that drink or combination is harmless or harmful, for the effects of alcoholic drinks are part of the folklore of society.

Alcohol and Other Drugs

Alcohol is synergic with other cerebral depressants and caution is required in administering hypnotics to people with high blood alcohol levels. When supplies of hypnotics are given to patients who are known to drink heavily, they should be warned to omit the hypnotic if they have been drinking. Deaths from this synergism may not be rare. Alcohol addicts, *i.e.* those with a developed tolerance to alcohol, are relatively less sensitive to some other cerebral depressant drugs (hydrocarbon anæsthetics and barbiturates), but of course the synergism with these drugs still occurs. There is no significant acquired cross-tolerance with the morphine group of drugs.

Miscellaneous Uses of Alcohol

In addition to those already mentioned is its use in strong solutions as an irritant which has given it a reputation as a restorative for fainting people. When such stimulation is indicated a slap in the face is just as irritant, cheaper, always handy and cannot enter the lungs and cause pneumonia. Alcohol precipitates protein and is used to harden the skin in bedridden patients. Local application also reduces sweating and may allay itching. As a skin antiseptic 70% by weight (76% by volume) is most effective. Stronger solutions are less effective. Alcohol injections are sometimes used to destroy nervous tissue in cases of intractable pain (trigeminal neuralgia, carcinoma involving nerves).

Another use for alcohol is as an antifoaming agent in treatment of acute pulmonary œdema where it, by altering surface tension, causes the bubbles to collapse (oxygen is bubbled through 95% ethanol and taken through a face mask). If given in this way it will be absorbed into the blood.

Methyl Alcohol

Methyl alcohol is of clinical importance because it is sometimes consumed as a substitute for ethanol. Its acute toxicity is slightly less than ethanol, that is, it makes the subject a little less "drunk", but it is metabolised at only about a fifth the rate of ethanol and it is the toxic metabolites produced over a long period which make methanol intoxication so serious.

Methanol poisoning may appear with or without initial symptoms similar to those of ethanol. There is severe malaise, vomiting and abdominal pain. Pancreatitis has been found at autopsy on poisoned patients and so morphine should not be used if it is avoidable (p. 159). Muscle cramps also occur. Coma and circulatory collapse may follow. A prominent symptom is visual disturbance with scotomata and total blindness, which may occur early or late. The mechanism is uncertain and partial or complete recovery can occur, although permanent blindness with optic atrophy is common. Very small doses can cause blindness and large doses sometimes have failed to do so, which has given rise to the suggestion that the eye changes may be due to an idiosyncrasy. They cannot be reliably reproduced in animals and so data are hard to obtain.

The characteristic symptoms of acute methanol poisoning may be delayed for many hours, or even a day or more if much ethanol has been consumed with it, as is often the case. This is because both alcohols are metabolised by the same enzymes and the rate at which each is metabolised depends on the amount of the other present, *i.e.* substrate competition. This can be made use of in treatment, the less toxic ethanol being added to delay metabolism of the methanol so that more of the latter is excreted unchanged in urine and breath so that the amount of metabolites formed is less, reducing the dangerous acidosis.

Methanol is metabolised into formaldehyde and then formate which produces an intense acidosis, combatting which is perhaps the most important feature of treatment.

There is reason to think that the prognosis depends chiefly on the acidosis, and this may be reversed by i.v. infusion of 5% sodium bicarbonate solution, of which substance over 100 G. in a few hours may be needed. One-sixth molar sodium lactate (1·87%) may be used instead. Obviously biochemical estimations of the plasma bicarbonate level and blood pH are of the greatest value in controlling therapy. In their absence, and in severe cases, it is better to risk overtreatment than undertreatment. Mild cases may be treated by oral administration. As methanol is so slowly metabolised a patient may relapse if sodium bicarbonate administration is stopped too soon.

Experiments in animals and clinical observations suggest that administration of ethanol to delay methanol metabolism is beneficial. It is suggested that about 100 ml. of ethyl alcohol should be given over each 24-hour period (say 15 ml. 4-hourly) but the dose must be regulated by the patient's response, in view of the fact that he probably has unknown amounts of various alcohols in him. A darkened room is reputed to influence the eye changes favourably and certainly can do no harm.

GUIDE TO FURTHER READING

On Drug Addiction

(1) Huxley, A. (1954). The Doors of Perception. London: Chatto and Windus.

(2) Maurer, D. W., and Vogel, V. H. (1954). Narcotics and Narcotic Addiction. Springfield: Thomas.

(3) Seevers, M. H. (1958). Drug addiction. *In* Pharmacology in Medicine. 2nd ed. Ed. V. A. Drill. New York: McGraw-Hill.

(4) De Quincey, T. Confessions of an English opium eater. First published in 1821.

On Tobacco

(1) Scott, R. B. (1952). Some medical aspects of tobacco smoking. *Brit. med. J.*, (*i*), 671.

(2) Burn, J. H. (1957). The pharmacology of smoking. *Proc. roy. Soc. Med.*, **50**, 500.

(3) Doll, R. (1957). Smoking and lung cancer. *Proc. roy. Soc. Med.*, **50**, 503.

(4) Fisher, R. A. (1958). Smoking and cancer. *Nature* (Lond.), **182**, 596.

(5) Oswald, N. (1957). Medical effects of smoking. *Proc. roy. Soc. Med.*, **50**, 504.

(6) Doll, R., Jones, F. A., and Pygott, F. (1958). Effect of smoking on the production and maintenance of gastric and duodenal ulcers. *Lancet*, (*i*), 657.

(7) Simon, O. L., *et al.* (1957). Immediate effect of chewing tobacco on circulation of habitual chewers. *J. Amer. med. Ass.*, **163**, 354.

(8) Russek, H. I., *et al.* (1955). Effects of tobacco and whiskey on the cardiovascular system. *J. Amer. med. Ass.*, **157**, 563.

(9) Buff, I. E. (1955). Effect of tobacco smoking in the normal person. *J. Amer. med. Ass.*, **157**, 569.

(10) Mackenzie, Compton (1957). Sublime Tobacco. London: Chatto and Windus.

(11) Burney, L. E. (1959). Smoking and lung cancer. A statement of the Public Health Service (U.S.A.). *J. Amer. med. Ass.*, **171**, 1829.

(12) Annotation (1959). A new angle on smoking. *Brit. med. J.*, (*ii*), 1465.

(13) Eysenck, H. J., *et al.* (1960). Smoking and personality. *Brit. med. J.*, (*i*), 1456.

On Alcohol

(1) Recognition of Intoxication (1958). London: British Medical Association.

(2) Thompson, G. N. (Editor) (1956). Alcoholism. Springfield: Thomas.

(3) Quarterly Journal of Studies on Alcohol. Newhaven: Laboratory of Applied Pharmacology, Yale University.

(4) Roe, O. (1955). The metabolism and toxicity of methanol. *Pharmacol. Rev.*, **7**, 399.

(5) Cohen, J., Dearnaley, E. J., and Hansel, C. E. M. (1958). The risk taken in driving under the influence of alcohol. *Brit. med. J.*, (*i*), 1438.

(6) Drew, G. C., Colquhoun, W. P., and Long, H. A. (1958). Effect of small doses of alcohol on a skill resembling driving. *Brit. med. J.*, (*ii*), 993.

(7) Newman, H. W. (1954). Emetic action of ethyl alcohol. *Arch. int. Med.*, **94**, 417.

(8) Report of B.M.A. committee on Alcohol and Road Accidents (1960). *Brit. med. J.*, (*i*), 269.

Chapter 10

DRUGS IN MENTAL DISORDER, PSYCHOTOMIMETICS

BACKGROUND TO THE USE OF DRUGS IN MENTAL DISORDER

WITH the increasing recognition of mental illnesses as a cause of disability, interest in the possibilities of drug therapy has naturally increased. The chemists have responded by making innumerable substances for investigation. One of the main snags has been the difficulty of predicting therapeutic efficacy from the animal experiments which must necessarily precede clinical trial; another is how to determine by clinical trial whether a genuine therapeutic effect has been achieved and if so whether it was in fact due to the drug. It is not surprising that no exact animal parallels for human mental disorders exist and that, as one pharmacologist working in the field has said, "the major problem of replicating in the laboratory the actions of potential tranquillisers in human psychoneuroses and neuroses remains almost completely unsolved" (*1*).

There is however great activity in this field for both the benefits to humanity and the financial rewards could be great, and laboratory workers are busy doing the best they can with experiments of an almost incredible variety (*1*). A therapeutic effect in human mental disease is hoped for if a chemical affects any part of the brain known to be related to behaviour; if it antagonises the effects of substances known to occur in the central nervous system, including adrenaline, 5-hydroxytryptamine and acetylcholine; if it antagonises substances which produce abnormal behaviour, *e.g.* mescaline, lysergic acid diethylamide, or if it modifies animal behaviour in so-called "experimental neuroses". This approach indicates how little is known of the pathological physiology of mental disorder.

Some of the animal techniques used to study the effects of chemicals on behaviour are: prevention of epileptic fits caused by sound (audiogenic fits) in mice; prevention of drug-induced convulsions; reduction of amphetamine toxicity; reduction of drug-induced hyperactivity in animals, modification of sham rage, modification of the shape of a spider's web and of the behaviour of Siamese fighting fish. There is also a wide range of "conditioning" methods which include administration of an unpleasant experience in place of the expected reward to an animal previously trained to perform a simple act to get food, so that it appears unhappy, and may show signs of anxiety which may be modified by drugs.

One of the difficulties of interpreting the results of animal experiments lies in the fact that it is impossible to know how an animal feels. For example, an animal may cease, after a drug, to show signs of the anxiety which had been induced in it during a conditioning experiment. The explanation may be that the drug is a true tranquilliser and has allayed anxiety selectively, leaving the animal virtually normal, or the animal might no longer show anxiety because it feels too ill or else has forgotten the recently learned routine so that the whole situation is different.

In laboratories where tranquillising drugs are sought it is usual to employ a number of tests simultaneously, so obvious is it that no one test can possibly be expected to reveal important new therapeutic agents. Attempts are also made to correlate animal experimental results with clinical efficacy. A drug shown clinically to be beneficial in, say, schizophrenia, would be carefully examined in a great many animal tests and those tests in which most activity was shown would be used as a battery for screening further new chemicals for possible clinical trial. Drugs for prospective therapeutic use in depressive states are sought by examining compounds for their effect on the spontaneous activity of small animals in cages suspended so that they respond to any movement of the occupant (jiggle-cages), or by counting the pecking frequency of pigeons, or by testing for antagonism of depressant drugs. It has not yet proved possible to make animals psychologically depressed.

The search along these lines for better drugs is reasonable on current knowledge, but it is an extremely crude process. The problems involved in psychiatry are more difficult than many other branches of medicine where animal experiments can often be devised to approximate to human disease. Animal experiments which throw light on the function of simpler nervous systems should not be despised, although care must obviously be taken to avoid over-enthusiastic extrapolation from them to man. Most of those working with these tests are acutely aware of the difficulties involved.

An alternative approach to the drug therapy of mental disease is the study of the biochemistry of human mental disorder. If characteristic metabolic abnormalities can be found in any disease then it may well become possible, in some cases, to make drugs that will modify or even rectify them. This may offer greater hope of therapeutic success in the psychoses in which behaviour differs qualitatively from normal, rather than in the neuroses in which it differs quantitatively.

When a drug is put up for clinical trial in mental disease, one of the principal difficulties is that it is not easy to find a homogeneous group of patients on whom to try it. Psychiatric diagnosis is less clearly defined than that in most other branches of medicine; indeed it has even been suggested that the usual criteria of what constitutes a "disease" may not be applicable in psychiatry. The performance of well-designed clinical trials in psychiatry also presents many difficulties, in the use of the double-blind technique, assessment of results and avoidance of interference by factors other than the drug under investigation. Unfortunately many published clinical studies, even a majority, are so designed that no conclusion can legitimately be drawn as to the value of the drug, although a conclusion commonly is drawn nonetheless. ". . . totally uncontrolled studies of the effects of a new drug, especially when the dependent variable is something as amorphous and elusive as anxiety, can be misleading. A striking testimonial to the validity of this statement is the way in which the popularity of new drugs typically runs through the well-documented cycle of panacea, poison, pedestrian remedy. The high incidence of uncontrolled studies is not a feature confined to drugs affecting behaviour. It seems characteristic of clinical research. . . .When one considers that the principles of the controlled experiment were written about by Bacon, in 1620, and Pascal in 1648 . . . , an examination of this literature in 1958 can be somewhat discouraging" (*3*).

Tranquillising drugs provide symptomatic treatment only; they do not affect basic disease processes but it is possible that by reducing a symptom, a vicious circle may be broken, which allows the patient to readjust himself and so to be "cured" at least temporarily. Reduction of symptoms may render a patient accessible to psychotherapy and so give benefit. The enthusiasm with which tranquillisers are welcomed by patients and used by doctors should give us pause. "Is it not possible that the use of these drugs represents a modern version of the 'furor therapeuticus'—a traditional 'occupational disease' of the physician? The last several decades have brought us, in rapid succession, various forms of 'shock treatments', psychosurgery, and, lastly, the tranquillising drugs. All have in common the fact that they provide socially sanctioned patterns of medical action and thus help the physician to do something when he is faced with a psychiatric problem" (*4*).

The physician is not treating the patient's disease alone when he gives a drug. He may be treating himself.

Tranquillisers and Stimulants

"Drugs are available which will increase the over-all output of patients with too little behaviour, and other drugs are available which reduce the output of patients with too much behaviour" (*8*). This bald statement usefully emphasises the depth of ignorance which is the most prominent feature of the background of the use of drugs to influence behaviour.

There is some evidence that all drugs which stimulate or depress the central nervous system are capable of impairing the performance of the individual. By means of cleverly designed tests it is possible to get some measure of qualities that might have been thought imponderable, such as incentive, vigilance and aspiration (5). It has been found that drugs can influence these in doses that produce no detectable effect to simpler examination. Whilst it would be alarmist to suggest that the use of these drugs, especially tranquillisers, can insidiously undermine the ability of skilled intellectual and physical performers, "it is nevertheless possible . . . that a little anxiety may indeed sometimes be an added incentive and help to do better, and that there is such a thing as being more relaxed than is good for efficiency. This would after all not be contrary to common sense" (5).

It is common ground, of course, that excessive anxiety destroys all skills and that depression is a bar to achievement.

Little definite is known about the effect of these drugs on car driving, but there is evidence that some tranquillisers in ordinary doses cause rather less impairment of performance in driving tests than do barbiturates in hypnotic doses. It can hardly be doubted that any drugs affecting the brain can, in large doses, adversely affect driving skill. The subject is treated more fully under alcohol (p. 190).

The two principal groups of drugs used in therapy of mental disease are:—

Tranquillisers

chlorpromazine (Largactil) & allied
  phenothiazine drugs
reserpine (Serpasil) & other
  rauwolfia alkaloids
mephenesin (Myanesin) &
  meprobamate (Miltown)
hydroxyzine (Atarax)
and
all hypnotics
alcohol
tobacco

Antidepressants or psychomotor stimulants

sympathomimetic amines, *e.g.*
  amphetamine (Benzedrine)
  dexamphetamine (Dexedrine)
methyl phenidate (Ritalin)
pipradrol (Meratran)
mono-amine oxidase inhibitors, *e.g.*
  iproniazid (Marsilid)
  pheniprazine (Cavodil)
  phenelzine (Nardil)
imipramine (Tofranil)
caffeine (p. 225)

Tranquillisers (p. 204). These drugs control hyperactivity and patients may feel relaxed when taking them. Drowsiness and fatigue are common side-effects, but unlike hypnotics which may also be effective "tranquillisers", the drugs do not behave as general anæsthetics. They are most efficient in hyperactive psychotic states and least in psychoneuroses.

Antidepressants and Psychomotor Stimulants (p. 207). These drugs are unhappily named for they are primarily antifatigue drugs, they do not specifically counter depression. Some depressed patients feel worse when taking them, but others, especially the milder cases, become more active and their mood alters so that they feel less depressed and sometimes even happy.

The effects of all drugs acting on mental processes vary greatly with the circumstances and the dose in which they are given.

Tranquillisers

Chlorpromazine (Largactil, Thorazine)

As a result of investigation of phenothiazine compounds for possible chemotherapeutic effect, first promethazine, the useful sedative and antihistaminic drug, was discovered and then chlorpromazine (1951). This illustrates what is still so often the case, that useful drugs are commonly found accidentally.

Chlorpromazine has a very large number of actions, but the mechanism of most of them is totally obscure. Practical therapeutics would be better served if the actions of chlorpromazine were distributed amongst three or four drugs instead of being concentrated in one. Its actions include:—

Central Nervous System Effects. There is a good deal of evidence that chlorpromazine acts in the hypothalamus and brain stem reticular formation. In animals chlorpromazine tames wild and angry monkeys and prevents the hyperthyroidism that ordinarily occurs in wild hares caught and exposed twice a day to barking dogs. It has a remarkable ability to control hyperactive and maniacal states without seriously impairing consciousness and it modifies the abnormal behaviour in schizophrenic states. It is ineffective against depression unless this is accompanied by agitation. Normal people often feel sleepy after taking chlorpromazine and it also induces some indifference to pain. In large doses chlorpromazine causes a Parkinsonian syndrome (as does reserpine), but small doses can sometimes relieve it. In moderate doses it controls the muscle spasm of tetanus, but very large doses may make the tetanus worse. This is probably an effect on the reticular formation where stimulation of one area activates, and of another depresses, spinal reflexes. Chlorpromazine also reduces muscle spasticity due to other neurological lesions. Epilepsy may be precipitated in predisposed people, but the drug has been used with success in epileptics with behaviour disorders.

Chlorpromazine is an anti-emetic effective against both drug and disease-induced vomiting, but is ineffective against motion sickness.

The Adrenergic Blocking Effect is moderately powerful and postural hypotension may occur as a side-effect. The peripheral vasodilatation induced by this action of chlorpromazine causes heat loss, and body temperature may fall as with other long-acting vasodilators, especially if the patient is anæsthetised. Some central effect on the temperature regulating mechanism is not excluded. The use of the term "artificial hibernation" in connection with the use of chlorpromazine with or without other drugs is particularly inappropriate for there is no general slowing down of bodily processes; if anything the circulation is more, not less, active.

Potentiation of Other Drugs by Chlorpromazine. Chlorpromazine potentiates all cerebral depressants including alcohol, analgesics, hypnotics and anæsthetics. This effect can have clinical importance, but usually only if the drugs are being used in large doses.

Miscellaneous Actions. Chlorpromazine has weak atropine-like, antihistaminic, ganglion-blocking and quinidine-like actions. It is a local analgesic but in solution it is very irritant.

Chlorpromazine is well absorbed from the alimentary tract and its action lasts about eight hours. It can be given deeply i.m. or i.v. It is probably chiefly metabolised in the liver.

Toxic Effects include excessive drowsiness, though the patient remains rousable; postural hypotension, dry mouth, and the Parkinsonian syndrome. Blood dyscrasias and rashes occur and occasionally lactorrhœa. The most serious toxic effect is jaundice, in which hepatic cellular damage is generally trivial, the principal impact being on the bile canaliculi which show cellular infiltration and biliary stasis. Jaundice seldom occurs within two weeks of starting the drug but relapse can occur at once on restarting it in a patient who has had chlorpromazine jaundice. This and its irregular occurrence suggest that it may be a hypersensitivity reaction. Recovery is almost invariably complete within a few weeks but permanent liver damage has been reported. Hepatic biopsy has revealed lesions in patients taking chlorpromazine who are yet free from jaundice. The possibility of liver damage or blood dyscrasia is sufficiently high to make casual use of chlorpromazine reprehensible.

Chlorpromazine is Used in mental disorders (see below), as an anti-emetic, to potentiate narcotics and to aid the production of hypothermia. It is used in severe pain both to potentiate other drugs and to induce indifference to pain by altering the emotional response. It can also be tried against intractable hiccoughs as may a very wide variety of drugs including carbon dioxide, pethidine, amphetamine, hyoscine, ganglion-blocking agents and mephenesin, which indicates that the pharmacology of hiccough is not understood.

The dose of chlorpromazine hydrochloride varies widely, from 25 mg. three times a day, orally, up to a total of a gram a day. By injection usual doses are 25 to 50 mg. i.v. or 50 to 100 mg. i.m., 4 to 8-hourly.

Other Phenothiazines

There is a great variety available. Although most of those advocated in psychiatry represent attempts to improve on chlorpromazine none has been shown definitely to be an all-round improvement. Their side-effects are essentially similar to those of chlorpromazine although they may differ in emphasis. Some of the newer compounds, such as promazine, have less adrenergic blocking effect and perhaps cause less drowsiness or jaundice. Some, such as perphenazine, are also liable to induce curious states of muscular rigidity (dystonia). If one phenothiazine gives a good therapeutic response marred only by side-effects it is worth trying another member of the group. Phenothiazines in use include: pecazine (Pacatal), perphenazine (Fentazin), thiopropazate (Dartalan), prochlorperazine (Stemetil), promazine (Sparine), acepromazine (Notensil), trifluoperazine (Stelazine). No doubt there are others.

Reserpine (Serpasil) and Deserpidine (Harmonyl)

These alkaloids of rauwolfia have two principal effects, hypotensive and tranquillising; both are probably exerted entirely in the central nervous system at least at therapeutic doses. Rauwolfia is discussed on pp. 275–277.

Mephenesin and Meprobamate

Mephenesin was accidentally found to paralyse voluntary movement in animals without depressing respiration. This action was exerted chiefly on spinal internuncial neurones or their synapses. In lower doses mephenesin also causes sedation. It has been found to be capable of reducing muscle spasticity and tetanus spasm, but the drug is rather impotent and very short-acting so that it has never had an important place in therapeutics. The solid is also poorly absorbed from the alimentary tract, although an alcoholic solution is marketed. Mephenesin given i.v. failed to provide satisfactory muscle relaxation for surgery; the dose needed for any effect at all was large and it caused hæmolysis if the solution strength was more than 1·5 to 2%.

Despite its numerous clinical disadvantages, the properties of mephenesin were of great interest and the possibilities of its type of action were evidently worth exploring. One result has been the introduction of meprobamate. This has similar effects and is active orally. Meprobamate, named "Miltown" after the town in the U.S.A. where it was made, has had a phenomenal sales success as a tranquilliser in the neuroses. In 1957 it was the commonest drug to be prescribed in the U.S.A. This success now appears to have been largely, if not entirely, unjustified (1). Despite its interesting pharmacology it has yet to be shown to be superior to barbiturates in the treatment of anxiety neuroses. Most of the published clinical work on meprobamate does not justify any conclusions at all. It can be used satisfactorily as a hypnotic. It is capable of reducing painful voluntary muscle spasm usefully. It may be that tense neurotics, who are known to have increased muscle tone, may feel better due to such relaxation.

Both mephenesin and meprobamate may control some cases of Parkinsonian tremor and in very high doses mephenesin can sometimes control myoclonic epilepsy and status epilepticus. The usual dose of meprobamate is 400 mg. three or four times a day. Addiction occurs; toxic effects include rashes, purpura (without thrombocytopenia), and other hypersensitivity reactions.

Drugs of this type are sometimes called "spinal cord depressants" or centrally-acting muscle relaxants, but their actions are not confined to the spinal cord, they certainly affect the brain stem reticular formation for example.

Hydroxyzine (Atarax)

Hydroxyzine is a depressant drug related to some antihistaminics. It does not quieten angry animals. It is of dubious value in therapeutics.

Azacyclonol (Frenquel)

Azacyclonol is an isomer of pipradrol but is a tranquilliser, whereas pipradrol is a psychomotor stimulant. It does not tame animals but does oppose the hallucinatory effects of mescaline and lysergic acid diethylamide in man. Azacyclonol has therefore been tried in hallucinated patients with the usual result that some reports are very enthusiastic and others state that the drug has no effect. Reported side-effects are trivial. The dose ranges from 20 to 100 mg. orally three or four times a day.

Benactyzine (Suavitil)

Benactyzine is an atropine-like drug which prevents animals minding when their expected reward in a conditioned reflex experiment is an unpleasant one. In man it interferes with the train of thought and causes forgetfulness. The evidence that it is beneficial in neuroses is tenuous.

Antidepressants or Psychomotor Stimulants

Sympathomimetic Amines (see also p. 249)

Amphetamine (racemic) and dexamphetamine (dextro-, the lævo-form is relatively inactive) are the principal drugs of this group used as mental stimulants. Their mode of action on the brain is unknown. Their peripheral actions are similar to those of ephedrine. Amphetamine will be described and its allies only in the ways in which they differ. As with all drugs acting on the central nervous system the psychological effects vary with mood and personality of the subject as well as with dose. The difference in response between children and adults is well illustrated by amphetamine (and ephedrine) for in children these drugs are generally sedative, not excitant. The following description can thus only be approximate.

The subject becomes both mentally and physically more active and fatigue is postponed (*12*). He may be more confident and show more initiative. He is better satisfied with a performance which has, in fact, deteriorated in accuracy as well as being more speedily accomplished. On the other hand there may be anxiety and a feeling of nervous and physical tension, especially with large doses, and the subject may show tremors and confusion, and feel dizzy. The sympathomimetic effect on the heart, causing palpitations, may also intensify the patient's discomfort or alarm. Acute poisoning may show itself in a hyperactive or even maniacal state not very dissimilar from a very hyperactive paranoid schizophrenia. Hallucinations sometimes occur. It is of interest that in mice the lethal dose of amphetamine is higher if the mice are caged separately than if they are caged in groups where their restlessness and excitement can be communicated to each other.

Addiction to amphetamine and to similar sympathomimetics occurs, but there is no definite abstinence syndrome, *i.e.* no physical dependence, and little tolerance, although emotional dependence is intense. Sometimes addicts use a barbiturate and amphetamine alternately.

It was noticed casually in 1937 that patients receiving amphetamine tended to lose weight. This was investigated in animals and man and found to be due to a reduction in voluntary food intake (*10*). Dogs would starve in the presence of food when given amphetamine, although they still showed interest in being fed and jealousy of the dog being fed before them. It was only when the food was actually placed in their cage that enthusiasm abated. Tolerance to the anorexic effect occurs.

Amphetamine, usually as the sulphate, has multifarious uses:—

As an antidepressant in mental disease (5 to 20 mg. orally 2 to 3 times a day)
Against mental fatigue (5 mg. 3-hourly)
Against physical fatigue (10 mg. 6-hourly)
To depress appetite in the treatment of obesity (5 to 10 mg. twice daily)
As a respiratory stimulant in hypnotic poisoning (see p. 110)
For its peripheral sympathomimetic effects (see p. 255)
Against narcolepsy

In Parkinsonism it may produce benefit used alone, but is best combined with other drugs

To antagonise depressant side-effects of other drugs, *e.g.* anticonvulsants, to enable adequate medication to continue

Miscellaneous; amphetamine is said to help some alcoholics to abstain; to be beneficial sometimes in tics and torticollis.

It has been advocated as an adjuvant in an extraordinarily wide variety of conditions, and may be worth trying in hiccoughs which have resisted everything else, in dysmenorrhœa, and in petit mal resistant to troxidone. In disturbed children with or without abnormal electroencephalograms amphetamine may improve behaviour, especially if the child is initially hyperactive.

More than very occasional use of amphetamine against fatigue is undesirable, as it promotes addiction and may lead to accidents. It cannot postpone fatigue indefinitely. Amphetamine should not be given after about 3 p.m., if it is desired to ensure a good night's sleep. Amphetamine can be given orally or by i.m. or i.v. injection. Acute amphetamine poisoning should be treated with sedatives, such as barbiturates and, if men are like mice, isolation may help. It is, of course, a clinical commonplace that quiet is desirable in any case of convulsant poisoning.

Dexamphetamine is similar to amphetamine but has about twice the potency. The oral dose of the sulphate is 2·5 to 10 mg.

Methamphetamine (Methedrine) is similar to amphetamine.

Phenmetrazine (Preludin) is similar to amphetamine and is chiefly used to reduce appetite (25 mg. orally two or three times a day). Addiction occurs.

Methyl Phenidate (Ritalin)

Methyl phenidate is a stimulant whose central effects are not obviously different from amphetamine. The oral dose of the hydrochloride is 10 mg. three times a day, but much more can be given.

Pipradrol (Meratran) differs insignificantly from methyl phenidate. The oral dose of the hydrochloride is 1 to 2 mg. three times a day.

Mono-amine Oxidase Inhibitors

Mono-amine oxidase is an enzyme concerned in the metabolism of adrenaline, noradrenaline and serotonin (5-hydroxytryptamine, 5-HT). When it is inhibited there is an increase of these amines in the central nervous system of experimental animals. In man, chemicals which inhibit mono-amine oxidase have powerful mental effects ranging from feelings of well-being and increased energy, to frank psychosis. Anxiety and agitation may be made worse. Drugs with this action, iproniazid

(Marsilid), pheniprazine (Cavodil) and phenelzine (Nardil) are being tried in the treatment of depression. Their place is by no means secure. Iproniazid is toxic to the liver and should be used, if at all, with the utmost caution. Claims that it is useful as a coronary vasodilator in angina pectoris have failed to convince.

Imipramine

Imipramine (Tofranil) is a drug which opposes the effects of 5-hydroxytryptamine in various test preparations. Its value in clinical practice is uncertain, but it has been found useful in depressive states, especially endogenous depression (*11*).

Choice of Drugs in Mental Disorders

The drugs are mentioned in approximate order of preference. Psychotherapy may often be preferable to drugs or else used concurrently.

Manic States. An injection of morphine and hyoscine is invaluable in controlling acute mania. As its effects wear off sedation may be continued by paraldehyde or barbiturates, or chlorpromazine may be used instead, especially for the milder cases. Reserpine can be effective but may take 2 to 4 hours to act even after i.m. injection. If the patient is in a single room, accompanied by a suitable nurse, smaller doses of depressant drugs will be needed, for excitement tends to subside sooner under these circumstances rather than in the presence of other patients, or if the patient is left entirely alone. Some maniacal patients are not quietened by very large doses of depressants until they suddenly collapse with respiratory depression.

Depression. Amphetamine or an allied sympathomimetic agent or methyl phenidate or imipramine or one of the other "antidepressants" listed can be useful. Depression may be made worse by chlorpromazine although some agitated depressives are helped by it. Reserpine is absolutely contra-indicated in depressive states. Agitated depression may benefit from barbiturate and amphetamine used together: Drinamyl Tablets contain dexamphetamine (5 mg.) and amylobarbitone (30 mg.).

Paranoid Psychoses may be helped by chlorpromazine or an allied phenothiazine derivative.

Schizophrenia. Chlorpromazine may greatly modify aggression, hyperactivity, delusional and hallucinated states. Reserpine is a second choice. Antidepression drugs may be needed.

Senile and Arteriosclerotic conditions in which patients are unco-operative and offensive are sometimes helped by chlorpromazine. These patients are commonly very sensitive to drugs and nocturnal delirium may be made worse by barbiturates.

Toxic Confusional States, *e.g.* delirium tremens, may be benefitted by chlorpromazine.

Aggressive Psychopaths are sometimes improved by œstrogens and amphetamine; the aggression need not necessarily take a sexual form to be benefitted by œstrogens.

Psychoneuroses. Apart from possible relief of anxiety or depression drugs probably offer no benefit. For anxiety and tension barbiturates (amylobarbitone or phenobarbitone) give results which have not been bettered by the newer tranquillisers, despite numerous claims to the contrary. Meprobamate may sometimes give as good results as barbiturates. Alcohol is, of course, highly effective, as the many neurotics who have become addicted testify. Obsessional and hysterical states are uninfluenced by drugs.

Drugs may also be used to remove specific symptoms which result from anxiety or tension and add to it by causing distress, *e.g.* propantheline for excessive sweating, meprobamate for excessive voluntary muscle tone.

Narcolepsy. Antidepressants usually give good results. Amphetamine or dexamphetamine should be tried first; large doses may be needed.

Naturally if any of the above conditions are worsened by insomnia then hypnotics may help, without themselves acting on the principal symptom.

Suicide and Drugs

It is not uncommon to have to prescribe sedative drugs for potentially suicidal outpatients. In such cases it is usual to prescribe minimal doses for short periods and, when the danger seems serious, to hand over the supply of drugs to a responsible person rather than to the patient. The hypnotic drug thalidomide (p. 107) might be considered for such patients.

PSYCHOTOMIMETIC DRUGS

These substances produce mental changes which resemble those of some psychotic states. The mechanism of action is unknown, but great interest has been aroused in the possibility of using them as tools for the investigation of mental disease and for testing new drugs planned for psychiatric use. The whole matter is empirical at present. The drugs include:—

Mescaline

Mescaline is an alkaloid from a Mexican cactus, the top of which is cut off and dried and used as "peyote buttons" in religious ceremonies. It induces a state not very unlike schizophrenia. Mescaline does not induce a true addiction and the drug has little importance except to members of some North and Central American tribes and to psychiatrists and biochemists who are interested in the mechanism of induced psychotic states. There has been a vogue amongst intellectuals for taking mescaline and publishing their experiences which was begun by Mr. Aldous Huxley.*

Lysergic Acid Diethylamide (LSD)

This substance induces a schizophrenia-like state not unlike that due to mescaline. Lysergic acid provides the nucleus of the ergot alkaloids and it was during a study of derivatives of this that in 1943 a Swiss research worker investigating LSD felt queer and had visual hallucinations. This led him to take a dose of the substance and so to discover its remarkable potency, the effective dose being about 30 micrograms.

Attempts have been made to use it as an aid to abreaction in psychotherapy but it is of experimental rather than of therapeutic importance.

Adrenochrome

Adrenochrome is an oxidation product of adrenaline. It can produce effects similar to those of mescaline and lysergic acid diethylamide, a fact that has led to speculation as to the possibility of its playing a role in mental disease.

Marihuana (Cannabis Indica, Hashish, Indian Hemp)

Marihuana has now no place in therapeutics, it is of importance only in the illegal drug trade. Marihuana induces a state of mental excitability with a feeling of well-being. There may be hallucinations and disorientation in time and space. The effects are extremely variable and it has a reputation as an aphrodisiac which is probably unjustified. It is also said to enhance appreciation of, and response to, auditory rhythm which has led to its use amongst a certain type of extempore musician. It is largely employed as a "spree drug", taken occasionally, and most users are not truly addicted to it. Tolerance is slight and physical dependence does not occur although psychic dependence may be strong. It is commonly taken by smoking "reefer" cigarettes. The plant grows wild in many countries including the Americas, the Near East and Asia, so that prevention of its illegal use is not easy.

GUIDE TO FURTHER READING ON DRUGS IN MENTAL DISORDER

(1) RILEY, H., and SPINKS, A. (1958). Biological assessment of tranquillisers. *J. Pharm.* (Lond.), **10**, 657.

(2) LAURENCE, D. R., and POND, D. A. (1958). The trade in tranquillity. *Brit. med. J.*, (*i*), 700.

---

* The Doors of Perception. London: Chatto & Windus, 1954.

(*3*) LATIES, V. G., and WEISS, B. (1958). A critical review of the efficacy of meprobamate (Miltown, Equanil) in the treatment of anxiety. *J. chron. Dis.*, **7**, 500.

(*4*) SZASZ, T. S. (1957). Some observations on the use of tranquilising drugs. *Arch. Neurol. Psychiat.* (Chicago), **77**, 86.

(*5*) STEINBERG, H. (1959). Effects of drugs on performance and incentives *In* Quantitative Methods in Human Pharmacology and Therapeutics. Ed. D. R. LAURENCE. London: Pergamon Press.

(*6*) VOGT, M. (1958). Pharmacology of tranquillising drugs. *Brit. med. J.*, (*ii*), 965.

(*7*) BEIN, H. J. (1956). The pharmacology of Rauwolfia. *Pharmacol. Rev.*, **8**, 435.

(*8*) DEWS, P. B. (1958). Drugs affecting behaviour. *In* Pharmacology in Medicine, 2nd ed. Ed. V. A. DRILL. New York: McGraw-Hill.

(*9*) WIKLER, A. (1957). The Relation of Psychiatry to Pharmacology. Baltimore: Williams Wilkins.

(*10*) HARRIS, S. C., IVY, A. C., and SEARLE, L. M. (1947). The mechanism of amphetamine-induced loss of weight. *J. Amer. med. Ass.*, **134**, 1468.

(*11*) BALL, J. R. B., and KILOH, L. G. (1959). A controlled trial of imipramine in treatment of depressive states. *Brit. med. J.*, (*ii*), 1052.

(*12*) CUTHBERTSON, D. P., and KNOX, J. A. C. (1947). The effect of analeptics on the fatigued subject. *J. Physiol.*, **106**, 42.

(*13*) Editorial (1959). Amphetamine in athletics. *Brit. med. J.*, (*ii*), 1464.

(*14*) SMITH, G. M., and BEECHER, H. K. (1960). Amphetamine, secobarbital, and athletic performance. *J. Amer. med. Ass.*, **172**, 1502.

(*15*) SAINSBURY, P., and LUCAS, C. J. (1959). Sequential methods applied to the study of prochlorperazine. *Brit. med. J.*, (*ii*), 737.

Chapter 11

ANTITUSSIVES, EXPECTORANTS, ANTI-EMETICS

COUGH

THERE are two sorts of cough, the useful and the useless. Cough is useful when it effectively expells secretions, exudates, transudates or extraneous material from the respiratory tract, *i.e.* when it is productive; it is useless when it is unproductive. Useful cough should be allowed to serve its purpose and should only be suppressed when it is exhausting the patient or his heart. Useless cough should be stopped, but if it is useless solely because there are thick secretions which cannot be expelled then expectorant drugs may be given to promote secretion of fluid in the respiratory tract so that the undesirable material may be made less tenacious and so more easily ejected.

Cough Suppression may be accomplished by modifying conditions on the mucous membrane. When cough arises due to irritation of the respiratory tract above the larynx then syrups and demulcent lozenges may be used, *e.g.* Liquorice Lozenges, B.P.C. Small children are prone to swallow lozenges and so a confection on a stick may be preferred.

When cough arises below the larynx steam inhalations often give relief. It is often desired to make the steam smell therapeutic and for this Benzoin Inhalation, B.P.C., or Friars' Balsam, may be added to the hot water. Benzoin inhalation may promote secretion of dilute mucus and so help to give a protective coating to inflamed mucous membrane, but its effects are more probably solely psychological.

Antitussive Agents Acting on the Central Nervous System

In general when it is desired to suppress cough, drugs acting on the medullary cough "centre" are used. Where these drugs are opiates then part of the effect may result from their actions on higher nervous centres. Psychic factors are well known to be important, as when during a silence in a theatre, the bored spectator feels an overwhelming desire to cough, but their importance in the cough of disease has been less appreciated.

Beecher and his colleagues have used patients with pathological cough, rather than normals with experimentally induced cough to study the action of antitussive agents. The first problem was to record cough frequency objectively, so that the actual amount of coughing could be compared with the opinions of the patient and his attendants. They used an apparatus which recorded cough by sound and automatically represented it as deflections on a moving paper. A number of drugs and dummy tablets were tested and it was discovered that although with codeine and heroin patients felt better, the actual frequency of cough had not significantly decreased (3). Naturally more evidence is needed before any definite conclusions are drawn, but it is clear that to imagine that opiate antitussive drugs act solely by suppressing a cough "centre" in the brain is altogether too simple.

All morphine-like drugs may be used in the control of cough. Those principally used are relatively non-addicting and have little depressant effect on the respiratory centre. They include codeine, pholcodine, hydrocodone, noscapine (narcotine), dextromethorphan (p. 166). It is possible that as good results can be obtained with these as with the more addicting substances, morphine, heroin and methadone which are powerful respiratory depressants. Preparations in the B.N.F. include Linctuses of Codeine, Pholcodine and Methadone. Codeine needs to be given in high doses, say 60 mg., and a tablet is perhaps preferable to the weak B.N.F. Linctus. A great many synthetic centrally acting non-narcotic antitussives are available. They include carbetapentane (Toclase), oxeladin (Pectamol), Becantyl, Sedulon and Taoryl. They have not rendered any of the older remedies obsolete.

Antitussive Agent Acting Peripherally

Benzonatate (Tessalon) is a local analgesic which appears to have a selective action on pulmonary stretch receptors. It is said to be an orally effective antitussive, especially useful in chronic cough associated with bronchospasm. The dose is 100 to 200 mg., three or four times a day, and maximum antitussive effect is delayed five to seven days after the start of therapy. Much more experience is needed before this interesting drug can be properly evaluated.

Expectorants

Expectorants are substances which increase the production of respiratory tract secretions. Those used clinically act in three ways: –

1. By setting up a reflex from the stomach and duodenum (iodide, ammonium chloride, acetates, ipecacuanha, guaiacols and creosotes or a hot drink such as Sodium Chloride Compound Mixture, B.P.C.).

2. By stimulating the bronchial secretory cells by an action unrelated to their cholinergic nerve supply (volatile oils, guaiacols and creosotes). Perhaps carbon dioxide should be included in this group. Inhalations of 5% carbon dioxide in oxygen (five to seven litres minute for five to 10 minutes, three to five times a day) through a mask or catheter, cause

liquefaction of secretions, increase respiratory movements and may dilate the bronchi. Carbon dioxide should not be used, of course, if the patient has pulmonary disease which itself has resulted in carbon dioxide retention. It can be dangerous if there has been recent hæmoptysis, because of the increased vigour of respiration.

3. By directly liquefying material in the bronchial lumen. Inhalations of various enzymes (trypsin, streptokinase-streptodornase) have been tried. They may however produce their principal effect by local irritation. Detergents (Alevaire) may reduce viscosity of secretions. These are all given by inhalation, and cannot be regarded as wholly accepted remedies.

General. Drugs which stimulate the vagus centre (*e.g.* centrally acting emetics) and choline drugs (which stimulate at the parasympathetic nerve endings on the glands) are expectorants which are not generally used clinically for the purpose because of their other undesired effects.

Reliable experimental data on expectorants are hard to come by. Many human experiments are contradictory and many animal experiments are irrelevant.

Some antihistaminics (promethazine, diphenhydramine) are offered as expectorants and antitussives. Such antitussive effect as they have is probably due to sedation, but gastric irritation may provide a mild expectorant effect.

Choice of Drug Therapy in Cough

Choice of drug therapy in cough depends on numerous factors. For example, cough due to invasion of a bronchus by a neoplasm requires different treatment from that due to chronic bronchitis with bronchospasm. As always, it is necessary to have a clear idea of what it is intended to achieve before starting to use drugs.

The following are general recommendations only; there is usually a wide choice of agents of approximately equal efficacy for any one case.

For simple suppression of useless cough: codeine, pholcodine, methadone (in that order of potency) in large infrequent doses. In children cough is nearly always useful and sedation at night is more effective to give rest than is codeine. Pertussis is an exception, sedation and atropine methonitrate may be used.

To increase bronchial secretion slightly and to liquefy what is there, steam inhalations with or without Benzoin Inhalation, B.P.C., and Sodium Chloride Compound Mixture, B.P.C., or Ammonia and Ipecacuanha Mixture, B.P.C. The irritant expectorants cause gastric pain if used for a long time. If a brisk increase in secretion is desired, large doses of iodide, 10 to 15 ml. of 6% potassium iodide 4 to 6 hourly and increased after two to three days for up to three weeks is probably the best way to get it, but side-effects may be unavoidable.

For cough originating in the pharyngeal region: glutinous sweets or lozenges.

If bronchospasm complicates cough then bronchodilator drugs (ephedrine, choline theophyllinate) should be used, although atropine may not be desirable as it thickens bronchial secretion. Oxygen inhalation also thickens secretion and patients having oxygen may need expectorants. The oxygen must be bubbled through water to avoid drying out the bronchi.

VOMITING, ANTI-EMETICS AND EMETICS

Numerous factors may activate the vomiting centre in the brain stem directly, reflexly through a nearby area called the chemoreceptor trigger zone, or via peripheral sensory receptors. If the cause cannot be removed it may be desirable to attempt to prevent or to suppress vomiting by drugs. The pharmacology of vomiting was little studied until the 1939 war, when motion sickness attained military importance because "when a landing has to be made in the face of resistance it is easy to see that seasickness might on occasion become a handicap". The British military authorities and the Medical Research Council therefore organised an investigation which has provided a type for many subsequent drug trials (*4*).

The aim was to find what drugs in what dose would prevent seasickness without interfering with physical and mental efficiency. The only guide to choice of drugs for the trial were the numerous claims based on uncontrolled observations in the past, which, however, made it clear that anticholine drugs (chiefly atropine and hyoscine) were likely to be important. Attempts to use swing sickness in the hope of being able to avoid "the disadvantage which the inconstancy of the sea imposed" were not satisfactory, as those who were sick on a swing were not necessarily sick at sea. Reluctantly the workers turned to the sea for their experiments, observing that "dependence on so fickle an element for experimental conditions imposed a considerable strain on the patience of the investigator. Chronic sufferers from seasickness may be astonished to learn that on most days through the year an obstinate and baffling calm haunts the waters round this island."

Whenever there was a prospect of sufficiently rough weather about 70 soldiers were sent to sea in small ships again and again, after being dosed with a drug or a dummy tablet and having had their mouths inspected to discourage attempts to dispose of the tablets by other means than by swallowing them. The ships returned to land when up to 40% of the soldiers vomited. "On the whole the men enjoyed the trips", some of them, however, thought the pills were given in order to make them vomit and some "believed firmly in the efficacy of the dummy tablets". It was concluded that, of the remedies tested, hyoscine (0·6 mg. or 1·2 mg.) was the most effective.

This study has been followed by very many others on the physiology and pharmacology of nausea and vomiting due to motion, drugs and disease.

Most of the effective anti-emetics have anticholine actions and are able to penetrate the central nervous system. Those anticholine drugs which are virtually unable to penetrate the central nervous system (*e.g.* quaternary ammonium derivatives) are generally ineffective. The fact that many useful anti-emetics are also antihistaminics is probably irrelevant. A single site of action for all anti-emetics has not been demonstrated, chlorpromazine has been shown to depress the chemoreceptor trigger zone, but some other anti-emetics do not. There is also a difference according to the cause of the vomiting, and drugs effective against motion sickness may be ineffective against vomiting of disease.

Motion Sickness

Motion sickness is more easily prevented than cured. Once it has started oral administration of drugs may fail, not only because they are vomited, but because the pylorus may be closed so that they cannot reach their site of absorption in the small intestine. Injections or suppositories are then to be preferred. It is as well to remember that prevention of motion sickness may only be possible at the expense of troublesome side-effects: sleepiness, dry mouth, blurred vision. A holidaymaker crossing from Dover to Calais by sea or flying from London to Paris in one-and-a-half hours or less may not be grateful for prophylaxis at such cost, especially if long-acting drugs like meclozine or promethazine are used. The duration of exposure is relevant to the choice of drugs; hyoscine is superior to other drugs for brief, but not for prolonged, exposure.

It is usual to take anti-emetics prophylactically 30-60 minutes before exposure to the undesired motion, but longer-acting drugs may be begun 12 to 24 hours before.

Very many drugs are effective, details of those most commonly used are given in the table on p. 219. A suitable choice would be meclozine or cyclizine (repeated) for prolonged and hyoscine or cyclizine for brief prophylaxis.

Protection rates are clearly likely to vary very much with the conditions of the trial, but up to 95% protection has been reported. Confident prediction of what will happen to any one subject about to take a drug of this kind for the first time is unwise, but naturally much may be gained by an assured air on the part of the prescriber, for it is common experience that motion sickness is very greatly influenced by psychological factors.

Other drugs which have some effect against motion sickness include buclizine, homatropine, chlorcyclizine. Barbiturates and amphetamine may be useful as adjuncts in therapy although they have insignificant anti-emetic effects of their own. Much may be done to prevent motion sickness by simple commonsense behaviour over meals and environment.

SOME DRUGS EFFECTIVE AGAINST MOTION SICKNESS

Non-proprietary name	*Proprietary names*	*Oral dose (no. of doses per day)*	*Remarks*
meclozine hydrochloride	Ancolan Bonamine Sea-legs	50 mg. (1)	Low incidence of side-effects. May cause sleepiness; good for prolonged prophylaxis.
promethazine hydrochloride	Phenergan	25 mg. (1)	Best taken in evening as sleepiness fairly common.
promethazine chlorotheophyllinate	Avomine	25 mg. (1)	Probably not superior to promethazine hydrochloride.
diphenhydramine hydrochloride	Benadryl	50 mg. (3)	May cause sleepiness.
dimenhydrinate	Dramamine	100 mg. (3)	The chlorotheophyllinate of diphenhydramine to which in equiv. dose, it is probably not superior. May cause sleepiness.
cyclizine hydrochloride	Marzine Marezine	50 mg. (3)	Low incidence of side-effects. May cause sleepiness. Good for prolonged prophylaxis.
hyoscine hydrobromide	Kwells Sereen tablets	0·6 mg. (3)	Useful in single dose for short journeys. Side-effects too troublesome for prolonged use. Atropine is probably equally effective.

These drugs all have anticholine effects and most happen to be antihistaminics too.

Vomiting Due to Drugs

Emetic drugs may act in the central nervous system on the chemoreceptor trigger zone (morphine and apomorphine), on the peripheral nervous system not associated with the intestine (veratum on vagal afferents) or in the gastro-intestinal tract. Digitalis and ipecacuanha probably act both in the central nervous system and in the gastro-intestinal tract. In general there is a paucity of definite evidence on how most drugs cause vomiting.

The best treatment of drug-induced vomiting is to withdraw or reduce the dose of the drug, but if this cannot be done an attempt, often unsatisfactory, may be made to oppose it by another drug. In general chlorpromazine, which is ineffective against motion sickness, is the best drug to try. However, in the case of vomiting due to morphine-like drugs diphenhydramine, dimenhydrinate and cyclizine are said to be better. Cerebral depressant effects of morphine and the anti-emetics are additive, and chlorpromazine potentiates morphine, so that caution is needed.

Chlorpromazine is useful against vomiting due to digitalis, alcohol, nitrogen mustard, antibiotics, emetine and aminophylline. A usual dose is 25 to 50 mg. of the hydrochloride orally, three times a day, but if vomiting has already begun the first dose at least may be given i.m. (25 mg.). Much bigger doses can be used.

Post-anæsthetic Vomiting (5)

This can be reduced by chlorpromazine, meclozine and cyclizine which may be given before or after the operation. Chlorpromazine potentiates anæsthetic agents and analgesics and hypnotics, and this must be taken into account when it is used. The sedative effects of meclozine and cyclizine are additive with those of other drugs.

Vomiting of Pregnancy

Meclozine may be the best drug; chlorpromazine is effective but side-effects are more common. Mild cases need no treatment. Pyridoxine (50 to 100 mg. a day in divided doses) is sometimes used. Evidence of its beneficial effect is only moderately impressive and its mode of action is unknown.

Vomiting Due to Disease

When removal of the cause is not possible this may be greatly helped by chlorpromazine, and occasionally by the other anti-emetic drugs.

Radiation Sickness is treated similarly to vomiting of pregnancy.

Other Anti-emetics

There are numerous new phenothiazine (chlorpromazine-like) drugs* and anticholine (and antihistaminic) drugs which are claimed to reduce vomiting from various causes. No doubt definitive trials will be done in due course and give confirmation or denial of these claims. Animal experiments do not give results which can reliably be applied to man. There are also many proprietary preparations containing sedatives, such as chlorbutol, which are recommended for motion sickness. Their value is dubious.

---

* Some may be superior to chlorpromazine as anti-emetics, causing less hypotension and less sedation.

Vertigo

An immense range of drugs has been recommended for vertigo. There is not yet enough knowledge of the physiology of the symptom for drug therapy to be on a scientific basis. All the anti-emetic drugs are used, also a hotch-potch of remedies whose variety indicates the absence of scientific evidence of their value, vasoconstrictors, vasodilators, central nervous system stimulants and depressants and, inevitably, vitamins. Perhaps simple sedation and an anti-emetic are most likely to help.

Therapeutic Emesis

Except in cases of poisoning therapeutic emesis is very rarely required. and even here it is better to cause vomiting by mechanical stimulation of the throat by the patient's *own* fingers or by using nauseous draughts of saline or mustard rather than emetic drugs. Apomorphine (2 to 8 mg. of the hydrochloride, s.c.) is a semisynthetic morphine-like alkaloid with the emetic action of morphine greatly enhanced. It also has the other central actions of morphine and can cause coma, especially if given to a patient whose central nervous system is already depressed. A second dose should never be given if the first fails, as it may. The drug is deservedly obsolescent. The amœbicide, emetine, illustrates the undesirability of naming drugs after their pharmacological properties. Innumerable other substances cause vomiting. A crude treatment of alcoholism is to give alcohol followed by an emetic to "condition" the patient against it. Of course no emetic should ever be administered to an unconscious patient.

Guide to Further Reading

On Antitussives and Expectorants

(*1*) Bickermann, H. A. (1960). The choice of antitussive agents. *In* Drugs of Choice, 1960-1961. Ed. W. Modell. St. Louis: Mosby.

(*2*) Boyd, E. M. (1954). Expectorants and respiratory tract fluid. *Pharmacol. Rev.*, **6**, 521.

(*3*) Gravenstein, J. S., Devloo, R. A., and Beecher, H. K. (1954). Effect of antitussive agents on experimental and pathological cough in man. *J. appl. Physiol.*, **7**, 119.

On Anti-emetics

(*1*) Borison, H. L., and Wang, S. C. (1953). Physiology and pharmacology of vomiting. *Pharmacol. Rev.*, **5**, 193.

(*2*) Report of a study by Army, Navy, Air Force Motion Sickness Team (1956). Evaluation of drugs for protection against motion sickness aboard transport ships. *J. Amer. med. Ass.*, **160**, 755.

(*3*) Chinn, H. I., and Smith, P. K. (1955). Motion sickness. *Pharmacol. Rev.*, **7**, 33.

(*4*) Holling, H. E., McArdle, B., and Trotter, W. R. (1944). Prevention of seasickness by drugs. *Lancet*, (*i*), 127.

(*5*) Bellville, J. W., Howland, W. S., and Bross, I. D. (1960). Postoperative nausea and vomiting. *J. Amer. med. Ass.*, **172**, 1488.

Chapter 12

ANALEPTICS

(Convulsant Stimulants of the Central Nervous System)

THESE drugs are suitable for acute vigorous stimulation of the central nervous system. They are relatively non-specific and are all convulsants and have little place in therapeutics except as antidotes to the respiratory depressant effects of drugs. Aminophylline and sympathomimetics such as amphetamine (p. 207) are exceptions in having a wider range of usefulness.

Leptazol acts throughout the whole central nervous system but its effect is strongest in the region of the mid-brain. The convulsions are predominantly clonic and only last a minute or two after a single i.v. injection. It has been used as a convulsant in mental disease but has been supplanted by electrical methods which are less unpleasant for the patient as well as being more convenient. It is active by mouth. Its use in barbiturate poisoning is discussed on p. 110.

Strychnine, a natural alkaloid, is valueless in therapeutics although it still survives in "tonics" and as a "bitter" to improve appetite, but cases of poisoning are sometimes seen. Strychnine convulsions are tonic and resemble those of tetanus, being due chiefly to a removal of inhibition from the spinal cord. They are reflex, *i.e.* occur in response to afferent stimulation, so that a victim of strychnine poisoning should be nursed like a case of tetanus. Mephenesin-like drugs are effective selective antidotes to strychnine in animals, but barbiturates i.m. or i.v. are more convenient in man, for the convulsions cannot last more than a few hours without death or recovery. Although both mephenesin and chlorpromazine can arrest tetanus convulsions, chlorpromazine is inactive against strychnine, which suggests that strychnine and tetanus are not as similar in their mechanism of action as has been thought. Massive oral doses of strychnine can cause rapid and sudden death without any convulsions. In strychnine poisoning the subject is conscious, and because of its cortical action, his special senses are heightened. The use of strychnine to improve the special senses is impracticable because doses which do this to any marked extent are too near the convulsant dose for safety.

Picrotoxin is obtained from an Asian plant. It is a powerful convulsant acting principally on the brain stem and spinal cord. The convulsions are clonic. Its only use in therapeutics is in the treatment of barbiturate poisoning (p. 110) and it may very well be dispensable even for that. It is given i.v. and a characteristic of its action is that there may be a delay of 15 minutes or more before its effects are seen. Convulsions due to picrotoxin may last half an hour or more. It should never be used in morphine poisoning for both drugs stimulate the spinal cord.

Picrotoxin was once used as a bitter in beer but was withdrawn as its pharmacology was clarified.

Nikethamide is widely used as a respiratory stimulant in, for instance, barbiturate poisoning or the respiratory failure of chronic bronchitis. Very large doses indeed can cause clonic convulsions. It is less effective than leptazol or picrotoxin and therefore safer. Although it is absorbed from the alimentary tract no significant effects can be got by that route, and as an oral tonic it is valueless. It can be given s.c., i.m. or i.v., 1 to 5 ml. of a 25% solution, although larger doses may be used. For continuous effect it should be given every 20 to 30 minutes. Nikethamide has a reputation for sobering alcoholics; if it is used for this purpose it should be borne in mind that its effects are briefer than those of alcohol and relapse may occur. The only action of nikethamide on the circulation results from stimulation of the vasomotor centre and is trivial. Nikethamide can cure pellagra, being a derivative of nicotinamide.

Bemegride is a convulsant which was introduced with the claim that it was a specific barbiturate antagonist. The claim was unfounded. It is probably not superior to other analeptics in barbiturate poisoning. Claims that it advantageously shortened the waking time after surgical operations under barbiturate have been both made and denied. One of the trials* was carried out on patients who had had a minor gynæcological operation under barbiturate anæsthesia. The experimenter had nikethamide, bemegride (50 mg.) and water put in ampoules so that he was unable to distinguish between them. After the operation one ampoule was injected. It was not possible, with 90 patients, to distinguish between the effects of any of the test solutions on the time taken for the patients to wake up. It is not easy consistently to decide when a patient has just awakened, for it is a gradual process, and knowledge of what drug has been given can easily introduce an unconscious bias, either against or for the drug, into the investigator's opinions. When a decision of this kind is to be made it is therefore especially desirable that the experiments should be done "blind" to eliminate any possibility of bias of this kind. A disadvantage of this particular experiment is that dosage of the analeptics could not be varied. On present knowledge it is not possible to be absolutely certain whether the claims that bemegride can shorten the waking time after barbiturate anæsthesia are valid or not, or, if they are, whether the drug is superior to other analeptics.

* Kaufman, L. (1958). *Anæsthesia*, **13**, 43.

Bemegride is short-acting and 50 mg. is injected i.v. every five to ten minutes. It is longer acting when given by mouth and attempts have been made to render barbiturate overdose impossible by incorporating some bemegride in the tablet. The merits of this process using this or other analeptics remain to be decided. It obviously might be useful in potentilly suicidal patients (see thalidomide, p. 107) but big doses of barbiturates can act for longer than bemegride.

Amiphenazole is another convulsant of which it was initially said that it should be used in barbiturate poisoning along with bemegride. As usual, good results were reported at first, but its use in this way is now so evidently unnecessary that it has been abandoned. An alternative use for amiphenazole has since been proposed. It may be given concurrently with morphine to patients with intractable pain to antagonise the sedative and respiratory depressant effects of morphine, thus allowing greater analgesia to be obtained by the use of higher dosage. Attempts have been made to use nalorphine similarly. It is possible that any analeptic may be used in this way but greater clinical experience is needed before it can be decided whether this is a generally useful practice. The oral dose of amiphenazole is 20 to 60 mg.

Vanillic Acid Diethylamide (Vandid) is another respiratory stimulant.

Lobeline is an alkaloid that stimulates respiration via carotid sinus chemoreceptors. It has a wide variety of other actions and is now obsolete although it was once extensively used in newborn children in the hope of discouraging pulmonary atelectasis by causing vigorous gasps and coughing which are characteristic of its effect.

Camphor is an obsolete convulsant.

Menthol is a convulsant which has never been used as an analeptic. Occasionally cases of poisoning occur as it is included in proprietary inhalations and "cold" remedies.

Thujone is a convulsant which used to be an important ingredient of absinthe.

Irritant Vapours, to be inhaled, have an analeptic effect in fainting, *e.g.* Aromatic Solution of Ammonia, B.P.C. (Sal Volatile). Nevertheless they sometimes "recall the exorbitant and deserting spirits to their proper stations" (Thomas Sydenham).

THE XANTHINES

(Caffeine, Theophylline, Theobromine)

These three compounds are obtained from plants. They are qualitatively similar but differ markedly in potency. Tea contains caffeine and theophylline. Coffee contains caffeine, and cocoa contains caffeine and theobromine. The cola nut ("cola" drinks) contains caffeine. Theobromine is weak and is of no clinical importance. Theophylline is generally used in the form of aminophylline, a combination with ethylenediamine.

The actions of caffeine and theophylline are:—

Central Nervous System Stimulation. Caffeine is more powerful than theophylline, but both drugs stimulate mental activity; thought is more rapid and fatigue is removed or its onset delayed. The effects on mental and physical performance vary according to the state and personality of the subject. Reaction-time is decreased. Performance that is inferior because of excessive anxiety may become worse. That the effects of caffeine are generally desired is shown by the remarkable popularity of caffeine-containing beverages throughout the world. Habitual tea and coffee drinkers are seldom willing to recognise that they may have a drug habit. Excessive chronic consumption of caffeine causes anxiety, restlessness, tremors, insomnia, headache and confusion. The existence of a true abstinence syndrome is doubtful. Both caffeine and theophylline are effective respiratory stimulants and will abolish Cheyne-Stokes respiration. In huge doses they cause convulsions.

On the Cardio-vascular System. Both drugs directly stimulate the myocardium and cause increased cardiac output, tachycardia and sometimes ectopic beats and palpitations. This effect occurs almost at once after i.v. injection and lasts half an hour. Theophylline may be used to relieve acute left ventricular failure. There is peripheral vasodilatation due to a direct action of the drugs on the blood vessels, but stimulation of the vasomotor centre tends to counter this. Changes in the blood pressure are therefore somewhat unpredictable. The cerebral circulation responds differently; the vessels constrict with consequent reduction of blood flow. Increased coronary artery blood flow occurs and is probably due to a mixture of the direct dilator effect on the vessels and a secondary response to increased myocardial activity. The utility of these drugs in angina pectoris is still debatable despite the fact that they were first advocated as long ago as 1895. Slow intravenous injection of caffeine or theophylline is essential because they are liable to cause a brisk hypotension, the cause of which is uncertain.

Smooth Muscle (other than vascular muscle which is discussed above) is relaxed. The only important clinical use for this action is in resistant cases of asthma (theophylline). Therapeutic effect is unpredictable but can be excellent.

On the Kidney. Diuresis (p. 311) occurs in normals, chiefly due to reduced tubular reabsorption. The drugs are hardly ever used for this purpose in therapeutics as superior agents are available, but no doubt the renal effect plays a small part in the diuretic response to theophylline in cardiac failure.

Miscellaneous Effects. Gastric secretion is increased and the basal metabolic rate may increase slightly.

Slight tolerance occurs. Caffeine and theophylline are readily absorbed from the alimentary tract including the rectum (suppositories of aminophylline are often used because the preparation is so irritant to the stomach). They are metabolised in the body.

Toxic Effects are extensions of the actions described above.

Uses of Caffeine and Theophylline

Caffeine is seldom used in therapeutics except as an ingredient of analgesic tablets, where it is thought to potentiate non-narcotic analgesics, but theophylline is valuable clinically.

The most generally useful preparation is aminophylline which is a salt of theophylline with ethylenediamine. Aminophylline is very irritant and because of this is often given i.v. (500 mg. over about 5 minutes in 25 ml. water), although sudden death may occur if it is given fast; i.m. injection is painful but some patients tolerate it. Patients are liable to vomit if given more than 300 mg. orally three times a day. Suppositories are available and may be useful, but can cause proctitis, especially if used more than twice a day. When given i.v. some of the observed respiratory stimulation is due to the ethylenediamine.

The principal uses of aminophylline are:—

In Paroxysmal Nocturnal Dyspnœa it is given i.v. for its immediate effect on the heart. Morphine may be given too, to prevent excessive respiratory stimulation. Its effect is brief but may be enough to terminate an attack.

When Diuretics Fail in heart failure aminophylline may, by improving renal blood flow, enable a diuresis to be established. It may be given i.v. 2 hours after the diuretic for this purpose.

When Digoxin given i.v. fails to improve severe heart failure in 1 hour aminophylline may be given i.v. for its cardiac effect, which is synergic with digoxin.

In Asthma aminophylline may occasionally prove useful when sympathomimetic drugs fail.

In the Dying Patient aminophylline i.v. may cause brief and unrepeatable recovery of consciousness and coherence.

In Angina Pectoris the value of aminophylline or its allies is doubtful.

Choline Theophyllinate (oxtriphylline, Choledyl)

Attempts to make non-irritant orally effective preparations of theophylline have resulted in choline theophyllinate which is reasonably effective. The dose is 100 to 400 mg. orally four times a day and it is mainly used to relieve bronchospasm.

Xanthine-containing Beverages

Cocoa never hurt anybody, probably because no one has ever drunk enough of it, but tea and coffee in excess can cause a syndrome similar to an anxiety state and exacerbation of peptic ulcer. Small children are not usually given tea and coffee because these drinks are considered bad for them, as, if strong, they contain substantial doses of caffeine, but cola drinks escape this prohibition. Normal children don't seem to need stimulating as do "normal" adults.

There is no evidence that these xanthines, although related chemically to uric acid, are harmful in gout. They are not converted to uric acid in the body. It is possible, on theoretical grounds, to make an imposing list of diseases which may be made worse by caffeine-containing drinks, but there is no conclusive evidence to warrant any general prohibitions.

Decaffeinated coffee, from which the caffeine has been extracted with trichloroethylene, is available for those who are kept awake by after-dinner coffee, but unfortunately it is rather expensive. There is immense individual variation in this effect of coffee both between individuals and sometimes in the same individual at different times of life.

Chapter 13

CHOLINES AND ANTICHOLINES

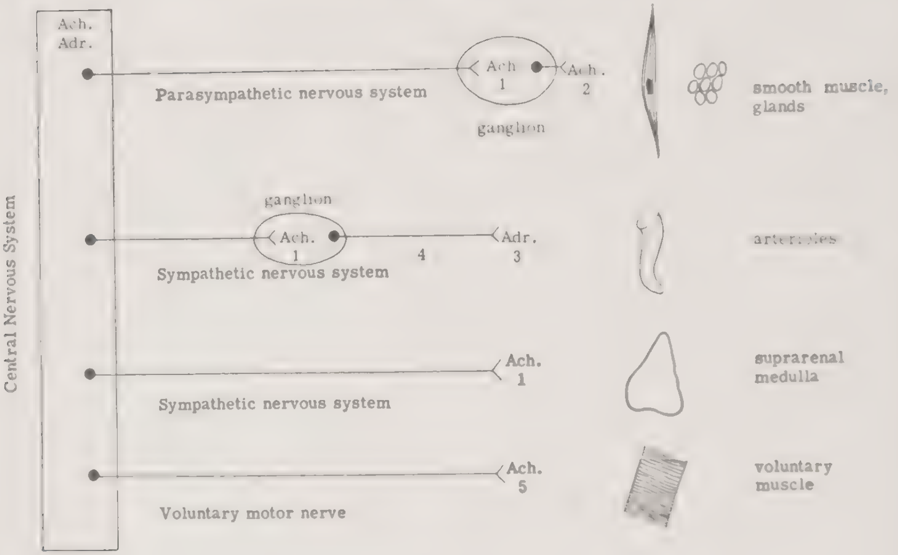


Diagram showing sites of chemical transmitters of nerve impulse.

Ach. = acetylcholine
Adr. = noradrenaline or adrenaline

Site 1 is blocked by ganglion-blocking agents and stimulated by big doses of choline esters and anticholinesterases.
Site 2 is blocked by atropine and stimulated by choline esters, anticholinesterases and pilocarpine.
Site 3 is blocked by adrenergic blocking agents and stimulated by sympathomimetic amines.
Site 4 is blocked by bretylium and guanethidine.
Site 5 is blocked by neuromuscular blocking agents and stimulated by choline esters and anticholinesterases.

CHOLINE DRUGS

(Also Known as Cholinergic Drugs)

These substances act at all the sites in the body where acetylcholine is the chemical transmitter of the nerve impulse. They first stimulate and sometimes later paralyse. In addition, like acetylcholine, they also act directly on peripheral blood vessels to dilate them.

Choline drugs may be:—

A. Choline esters (carbachol, methacholine) which act at all sites like acetylcholine.

B. Alkaloids (pilocarpine, muscarine) which act directly on end-organs affected by acetylcholine.

C. Cholinesterase inhibitors, or anticholinesterases (physostigmine, neostigmine), which inactivate the enzyme which destroys acetylcholine, allowing the chemical transmitter to persist and produce intensified effects.

Choline drugs act at the following sites:—

Autonomic Nervous System
PARASYMPATHETIC DIVISION
  ganglia
  post-ganglionic endings
SYMPATHETIC DIVISION
  ganglia
Neuromuscular Junction
Central Nervous System
Blood Vessels, chiefly arterioles

Acetylcholine is the chemical transmitter of the nerve impulse at all these sites of action except on blood vessels. The action of choline drugs on blood vessels is mainly direct and unrelated to cholinergic vasodilator nerves. A list of principal effects is given below. Not all occur with every drug and not all are noticeable at therapeutic doses. For example, methacholine does not stimulate autonomic ganglia and central nervous system effects of choline drugs are best seen in cases of anticholinesterase poisoning. Atropine antagonises all the effects of choline drugs except those at autonomic ganglia and the neuromuscular junction.

Choline Drugs on the Autonomic Nervous System

PARASYMPATHETIC DIVISION. Stimulation of both the cholinergic synapses in ganglia and the post-ganglionic endings affects chiefly the following organs:—

The eye: Miosis and spasm of the ciliary muscle occur so that the eye is accommodated for near vision. Intra-ocular pressure falls due probably to vasodilatation in vessels at the point where intra-ocular fluids drain into the blood.

The exocrine glands: There is increased secretion, most noticeably of the salivary, lachrymal, bronchial and sweat glands. The last are mostly cholinergic although anatomically part of the sympathetic system; some sweat glands may be adrenergic.

The heart: Bradycardia occurs, with auriculo-ventricular block and eventually cardiac arrest. The stroke volume is decreased.

The bronchi: Bronchoconstriction occurs, and combined with the increased secretion this may be serious in asthmatic or other allergic subjects, in whom choline drugs should be used with caution.

The alimentary tract: There is increased movement and secretion and colicy pain may occur. The patient may defæcate.

The bladder and ureters contract and the drugs promote micturition.

Sympathetic Division. The ganglia only are stimulated, also the cholinergic nerve to the adrenal medulla. These effects are overshadowed by effects of the drugs on the parasympathetic system and are commonly only evident if atropine has been given to block these, when tachycardia, vasoconstriction and hypertension occur.

Choline Drugs on the Neuromuscular Junction

The neuromuscular junction has a cholinergic nerve ending and so is stimulated, causing muscle fasciculation followed, if excess is given, by a depolarisation neuromuscular block.

Choline Drugs on the Central Nervous System

There is usually stimulation followed by depression, but there is great variation between drugs, possibly largely due to differences in penetration into the nervous system. Mental excitement occurs, with confusion and restlessness, insomnia (with nightmares when sleep does come), tremors and dysarthria, and sometimes even convulsions and coma.

Choline Drugs on the Blood Vessels

There is stimulation of cholinergic vasodilator nerve endings in addition to the more important direct dilating action on arterioles and capillaries. Anticholinesterases potentiate acetylcholine which exists in the vessel walls.

Nicotinic and Muscarinic Effects

The actions at autonomic ganglia and the neuromuscular junction (*i.e.* at the end of cholinergic nerve fibres which arise in the central nervous system) are described by pharmacologists as "nicotinic" because they are like the stimulant effects of nicotine. The actions at post-ganglionic cholinergic endings (parasympathetic endings plus the cholinergic sympathetic nerves to the sweat glands) and those direct on blood vessels are described as "muscarinic" because they resemble those of the alkaloid muscarine. The central nervous system actions are not included in this categorisation. The terms are useful because it is more concise to say, for example, that atropine blocks the muscarinic but not the nicotinic effects of neostigmine than it is to describe this antagonism in any other way. But these terms seem to be unacceptable to clinicians who, although they were nearly all brought up on them, decline to apply them when discussing the clinical use of drugs, perhaps because they find them unnecessary as well as confusing, despite the fact that they were introduced to avoid confusion; they will therefore not be used here. (For nicotine, see p. 187.)

Acetylcholine

Since acetylcholine has such great importance in the body it is not surprising that attempts have been made to use it in therapeutics. In fact a substance with such a huge variety of effects and so rapidly destroyed in the body is unlikely to be useful in therapy.

The use of acetylcholine in psychiatry illustrates some facets of the introduction of new remedies as well as providing interesting clinical pharmacological data. It was first injected intravenously as a therapeutic convulsant in 1939, in the justified expectation that the fits would be less liable to cause fractures than those following therapeutic leptazol convulsions. Recovery rates of up to 80% were claimed in various psychotic conditions. Enthusiasm began to wane however when it was shown that the fits were due to anoxia resulting from cardiac arrest and not to pharmacological effects in the brain (*1*). The following composite description of the effects of intravenous injection on many patients shows a mixture of direct effects of acetylcholine and of anoxia due to acetylcholine-induced cardiac arrest: A few seconds after the injection (which was given as rapidly as possible to avoid total destruction in the blood) the patient sat up "with the knees drawn up to the chest, the arms flexed and the head bent forward. There were repeated violent coughs, sometimes with flushing. Forced swallowing and loud peristaltic rumblings could be heard." Respiration was laboured and irregular. "The coughing abated as the patient sank back in the bed. Forty seconds after injection the radial and apical pulse were zero and the patient became comatose." The pupils dilated, and deep reflexes were hyperactive. In 45 seconds the patient went into opisthotonos with brief apnœa. Lachrymation, sweating and borborygmi were prominent. The deep reflexes became diminished. The patient then relaxed and "lay quietly in bed—cold moist and gray. In about 90 seconds flushing of the face marked the return of the pulse." The respiratory rate rose and consciousness returned in about 125 seconds. The patients sometimes micturated but did not defæcate. They "tended to lie quietly in bed after the treatment". "Most of the patients were reluctant to be treated" (*2*).

The investigators who did this series obtained bad therapeutic results except in one schizophrenic who very nearly died. In this patient the pulse first disappeared for 50 seconds, returned for 20 seconds and disappeared again for 140 seconds. It then reappeared for 5 and disappeared for the following 50 seconds, after which the patient "recovered". The authors considered that the brain had suffered such extensive anoxic damage "that obvious schizophrenic symptoms, at least for the time being, (were) impossible."

These and other results were sufficiently intimidating for therapy to be modified to non-convulsant doses for neurotics. After several favourable reports a careful study was done in which it was shown that acetylcholine was not a therapeutic agent because the same rate of improvement occurred in control groups, the use of control groups having been neglected by those who popularised the treatment. The authors of this series commented on the necessity for a placebo or dummy in controlled therapeutic trials as being "nowhere more true than where psychiatric practice is concerned, because a substantial proportion of emotionally disturbed patients show favourable responses to any therapeutic effort which combines enthusiasm, impressiveness and benevolence" (*3c*).

As it would clearly be very useful to the physician to be able to produce some of the effects of acetylcholine without all the others, related substances have been investigated and there is now a variety of substances available with longer action and varying degrees of selectivity; but none confine their effects to one organ alone. The principal are described below.

Other Choline Esters

Methacholine is destroyed by cholinesterase less rapidly than acetylcholine. It is potentiated by anticholinesterase drugs. The effects are predominantly cardiovascular and last up to 30 minutes after 10 to 30 mg. of the chloride or bromide, s.c. It is unreliable when given by mouth (50 to 100 mg.), being largely destroyed in the intestine. Methacholine is used to stop supraventricular tachycardias (p. 299) and to stimulate bowel and bladder, although carbachol may be preferable for this. When it is used atropine sulphate (0·5 to 2 mg. i.v. or s.c.) should be available in case it is needed to stop dangerous cardiac effects (bradycardia and cardiac arrest).

Carbachol is a choline ester which is not destroyed by cholinesterase, so that its effects are synergic with anticholinesterases; there is no potentiation as with methacholine. Carbachol is both more potent and longer acting than methacholine and its actions are more pronounced on the bladder and bowels, so that it is usual in clinical practice to use methacholine for cardiac effects and carbachol for bowel and bladder stimulation.

Carbachol is given s.c. (0·2 to 0·5 mg.) or orally (1·2 to 1·8 mg.); unlike methacholine it is stable in the alimentary tract. Both carbachol and methacholine are extremely dangerous if given intravenously.

Bethanechol (Urecholine, Mechothane) is related to methacholine but it is not destroyed by cholinesterase. It acts chiefly on the bowel and bladder. The dose of the chloride is 2 to 5 mg., s.c., or 5 to 30 mg. by mouth.

Alkaloids with Choline-like Effects

Pilocarpine is an alkaloid from an American plant. It acts directly on end-organs innervated by post-ganglionic cholinergic nerves (parasympathetic system plus sweat glands); it also stimulates and then depresses the central nervous system. Its action at the neuromuscular junction and autonomic ganglia is very slight. Its chief clinical use is in the eye as a miotic (1% solution of the nitrate). It has a totally undeserved reputation as a hair restorer but is very occasionally useful as a sialogogue in patients taking large doses of atropine. Objectionable effects such as sweating often more than counterbalance the benefits. Overdose is liable to cause respiratory symptoms due to bronchospasm and profuse bronchial secretion.

Arecoline is an alkaloid in the betel nut which is chewed in the East and forms a drug habit, for like other parasympathomimetic drugs it stimulates the brain. It has the actions of acetylcholine and has no place in therapeutics.

Muscarine is of no therapeutic importance, but cases of poisoning occur when the fungus (Amanita muscaria, fly agaric, so called because it was used to poison the common fly, muscus domesticus) which contains it is eaten. The effects are those of stimulation of all end-organs innervated by post-ganglionic cholinergic nerves. In addition it causes vasodilatation and stimulates the central nervous system. All these effects are antagonised by atropine.

The lengths to which man is prepared to go in taking "chemical vacations" from life if conditions are hard are shown by the inhabitants of Eastern Siberia who used the fungus habitually for its cerebral stimulant effects. They were apparently prepared to put up with the autonomic actions to escape briefly from reality. The fungus was very scarce in winter when, no doubt, the greatest need for it was felt and the frugal devotees discovered that by drinking their own urine they could recover some of the alkaloid. Unfortunately cheap alcohol has supplanted most such interesting habits and addictions.

It is convenient to deal here with the effects of eating poisonous fungi. They are usually described as "mushroom" poisoning although mushrooms are not poisonous, but merely relatively indigestible.

"Mushroom" Poisoning

There are three principal clinical pictures:—

EARLY ONSET. Choline ("muscarinic", p. 230) effects occur in less than two hours. This is typical of Amanita muscaria poisoning. The treatment is on general principles and large doses of atropine.

Late Onset. Abdominal pain, vomiting and diarrhœa occur more than five hours after ingestion. This is typical of Amanita phalloides poisoning. Later there are signs of acute liver and renal damage. There may be severe hypoglycæmia and electrolyte disturbances. Death is common. Treatment is on general principles.

Non-specific Gastro-enteritis.

It is evident that it may not be easy to distinguish the three kinds early on.

Anticholinesterases

At cholinergic synapses and in erythrocytes there is an enzyme specific for the destruction of acetylcholine, "true" cholinesterase or acetylcholinesterase. In various tissues, especially blood plasma, there are other esterases which are not specific for acetylcholine but which also destroy other esters, e.g. procaine. These are called "non-specific" or "pseudo" cholinesterases. Chemicals which inactivate these esterases (anticholinesterases) are used in medicine and agriculture. They act by allowing naturally formed acetylcholine to accumulate instead of being destroyed and their effects are almost entirely due to this accumulation in the central nervous system, at the neuromuscular junction, autonomic ganglia, post-ganglionic cholinergic nerve endings (which are principally part of the parasympathetic nervous system) and in the walls of blood vessels where acetylcholine is not necessarily associated with nerve endings. Some of these effects oppose each other, for instance the effect of an anticholinesterase on the heart will be the resultant of stimulation at sympathetic ganglia and the opposing effect of stimulation at vagal ganglia and post-ganglionic nerve endings. Therefore the clinical effects of anticholinesterases are not entirely predictable. Anticholinesterases of course increase the effect of all choline drugs.

Anticholinesterase Poisoning

The anticholinesterases used in therapeutics are generally those which reversibly inactivate cholinesterase for a few hours. Those (organo-phosphates) which inactivate it almost or completely irreversibly, so that recovery depends on formation of fresh enzyme, which takes weeks, have been found suitable for use as agricultural insecticides and have been studied for use in war ("nerve gas"). Cases of poisoning are therefore likely to be met outside therapeutic practice. Diagnosis depends on observing a substantial part of the list of actions on pp. 229–230. The prominence of individual effects varies with different drugs, e.g. sweating and salivation are not usual with dyflos poisoning.

Death is due to a combination of the actions in the central nervous system, to paralysis of the respiratory muscles by peripheral neuromuscular block, and to pulmonary œdema and bronchial obstruction due to circulatory and bronchial secretory changes; these together may culminate in respiratory failure. The central effects, and those due to stimulation at post-ganglionic cholinergic nerve endings and vasodilatation, are antagonised by atropine. The neuromuscular block is not, for atropine does not antagonise acetylcholine at the endings of nerve fibres which arise in the central nervous system.

Poisoning by those drugs which are reversible inhibitors may be treated with atropine in large doses (1 to 5 mg. of the sulphate, i.m. or i.v.) and by artificial respiration if necessary. Poisoning by the organophosphate irreversible cholinesterase inhibitors presents an even more serious therapeutic problem. If poisoning is due to absorption through the skin then thorough washing is essential, but even so it may be impossible to prevent further absorption. Atropine is given as above, hourly, until signs of atropinisation appear. One of the new specific antidotes should also be administered. These are substances developed since it was discovered that the organophosphate compounds inactivate cholinesterase by phosphorylating the active centre of the enzyme. They are either themselves phosphorylated very easily and so compete for the poison in the body, diverting it from cholinesterase, or else they dephosphorylate the enzyme. The principal specific antidotes available are oximes, P2S and PAM (i.m. dose 1 to 2 G.). One dose is usually enough, but in the case of parathion, which is slowly converted into an active substance after it enters the body, further doses may be required.

Anticholinesterase Drugs

Physostigmine (eserine) is an alkaloid, obtained from seeds of a West African plant, which has long been used as both a weapon and as an ordeal poison.* It acts for a few hours and its therapeutic use is confined to the eye (in which it causes miosis, spasm of the ciliary muscle and reduced intra-ocular pressure) since it is less reliable systemically than neostigmine.

Neostigmine is a synthetic anticholinesterase whose actions are more prominent on the neuromuscular junction and the alimentary tract than on the cardiovascular system and eye. It is therefore principally used in myasthenia gravis and to stimulate the bowels and bladder (in patients taking ganglion-blocking agents, and with atonic bowels or bladder after surgery), and as an antidote to neuromuscular blocking agents which act by competition. In addition it has a direct stimulating action on the motor endplate, unrelated to inhibition of cholinesterase, and this may be of importance in myasthenia gravis. Neostigmine as the bromide is

* Annotation (1953). Primitive poisons. *Lancet*, (*i*), 1036.

effective orally (15 to 30 mg., three or four times a day), and as the methylsulphate by injection (usually s.c.) 0·25 to 1 mg. But higher doses may be used, often combined with atropine, in myasthenia gravis.

Neostigmine has been advocated for the relief of muscle spasm in a variety of diseases. The claims are ill-substantiated. It may produce an effect in the spinal cord, depressing multineuronal reflexes by allowing excessive accumulation of acetylcholine to produce depolarisation block.

Pyridostigmine (Mestinon) is similar to neostigmine but has a slower onset and slightly longer duration of action. It is often used for myasthenia gravis. 4 mg. of the bromide are equivalent to 1 mg. neostigmine bromide.

Benzpyrinium (Stigmonene) has no advantages over neostigmine.

Edrophonium (Tensilon) is related to neostigmine. It is a very short-acting anticholinesterase, with, in addition, direct stimulant effects at the neuromuscular junction, for which site it is comparatively selective. Autonomic effects are minimal and are usually only marked at high doses. Over-dose causes neuromuscular block. Its action, after 3 mg. of the chloride i.v. is over within five minutes, which is too short to make it a useful antidote to competitive neuromuscular blocking agents. It is chiefly used in the diagnosis of myasthenia gravis.

Dyflos (DFP or diisopropyl fluorophosphate) is one of the many organophosphates which are powerful and long-acting anticholinesterases, the duration of whose effects is limited more by synthesis of new cholinesterase than by freeing of inactivated enzyme. The effects in man may last for two weeks or more, which render it unsuitable for systemic use. All very long-acting drugs tend to be difficult to control if they are very potent, and this makes them dangerous. Dyflos is used solely in the eye as a miotic, 0·1% solution in arachis oil. Spasm of the ciliary muscle may be intense and cause headache. It should be handled with caution and spilling and inhalation of the vapour avoided as, like similar compounds, it can be absorbed by any route. It would qualify as suitable for chemical warfare if even more noxious anticholinesterases had not been discovered: TEPP (tetraethyl pyrophosphate), HETP (hexaethyl tetraphosphate), OMPA (octamethyl pyrophosphoramide), parathion and sarin. These substances are absorbed through the skin as well as by other routes.

Myasthenia Gravis

In patients with this disease it has been found that choline (which normally depolarises the motor endplate), can compete with acetylcholine at the motor endplate and cause neuromuscular block, i.e., a product of the breakdown of acetylcholine can produce a curare-like (competitive) neuromuscular block. Other evidence that a characteristic of myasthenia gravis is an abnormality in the response of the motor endplate is found in the fact that decamethonium, after initial depolarisation, also causes a competitive or curare-like block. Experiments on animals suggest that acetylcholine is also capable, in certain circumstances, of exerting a curare-like effect, *i.e.* acetylcholine can block itself (*6*).

The practical implications of these observations are not yet clear, but it may be that there is an abnormality of the motor endplate in myasthenia such that larger amounts of acetylcholine are needed to produce normal muscular contraction than in normals. Ordinarily the disease is treated by neostigmine orally. Neostigmine was introduced into clinical practice in 1931 for its stimulant effects on intestinal activity. In 1934 it occurred to Dr. Mary Walker that since the paralysis of myasthenia had been attributed to a curare-like substance in the blood, physostigmine (eserine), an anticholinesterase drug known to antagonise curare, might be beneficial. It was, and she reported this important observation in a short letter.* Soon after this she used neostigmine by mouth with greater benefit.

The sudden appearance of an effective treatment for a hitherto untreatable chronic disease must always be a dramatic event for its victims. The impact of the discovery of the action of neostigmine has been described by one patient.

"My myasthenia started in 1925, when I was 18. For several months it consisted of double-vision and fatigue. . . . An ophthalmic surgeon . . . prescribed glasses with a prism. Soon, however, more alarming symptoms began." Her limbs became weak and she "was sent to an eminent neurologist. This was a horrible experience. He . . . could find no physical signs . . . declared me to be suffering from hysteria and asked me what was on my mind. When I answered, truthfully, that nothing was except anxiety over my symptoms, he replied, 'My dear child, I am not a perfect fool . . . ' and showed me out." She became worse, and at times she was unable to turn over in bed. Eating and even speaking were difficult. Eventually her fiancé, a medical student, read about myasthenia gravis and she was correctly diagnosed in 1927. "*There was at that time no known treatment and therefore many things to try.*" She had gold injections, thyroid, suprarenal extract, lecithin, glycine and ephedrine. The last had a slight effect. "Then in February 1935, came the day that I shall always remember. I was living alone with a nurse . . . . It was one of my better days, and I was lying on the sofa after tea . . . . My fiancé came in rather late saying that he had something new for me to try. My first thought was, 'Oh bother! Another injection, and another false hope.' I submitted to the injection with complete indifference, and within a few minutes began to feel very strange . . . when I lifted my arms, exerting the effort to which I had become accustomed, they shot into the air . . . every movement I attempted was grotesquely magnified until

---

* Walker, M. B. (1934). *Lancet, (i)*, 1200.

I learnt to make less effort . . . it was strange, wonderful, and at first very frightening . . . we danced twice round the carpet. That was my first meeting with neostigmine, and we have never since been separated."*

Anticholinesterase drugs are also used in the diagnosis of myasthenia gravis. If the weakness and fatiguability are dramatically relieved then the diagnosis is confirmed; 1 to 3 mg. neostigmine methylsulphate may be injected s.c. It is generally best to give 0·5 mg. atropine sulphate for each 1 mg. neostigmine methylsulphate to avoid visceral side-effects, *e.g.* colic, due to stimulation of the parasympathetic autonomic system. The atropine does not interfere with the effect of neostigmine at the neuromuscular junction. A failure to improve dramatically does not prove the patient has not myasthenia gravis, as a few cases respond poorly. Edrophonium has fewer autonomic side-effects and a much briefer action than neostigmine. A syringe is loaded with 10 mg. of the chloride; 2 mg. are given i.v. and if there is no reaction in 30 seconds the rest is injected. An hour later 15 or 20 mg. can be given if there was no response to the first injection.

Treatment of the disease is usually by neostigmine bromide, 15 to 75 mg. a day, or by pyridostigmine bromide, 60 to 300 mg. a day, in three or four doses orally. Much higher doses may be needed however.

The chief differences between these drugs are that pyridostigmine has a longer action, so that patients may be less weak on waking in the morning, and causes fewer visceral side-effects so that concurrent administration of atropine may be needed less often. Ephedrine enhances neuromuscular conduction and may be useful too. Too high a dose of anticholinesterase drugs may make the weakness worse (cholinergic crisis) and it is important to distinguish this from an exacerbation of the disease (myasthenic crisis). There is no simple means of making this distinction, but an injection of 2 mg. edrophonium chloride will, if therapy is inadequate, transiently increase strength, whilst if therapy is excessive it will increase weakness in addition to causing parasympathomimetic side-effects. This test should not be undertaken lightly. The habitual use of atropine to abolish parasympathetic effects is undesirable because it may mask excessive therapy, and so make the differentiation between myasthenic and cholinergic crisis more difficult.† In the absence of atropine, parasympathomimetic side-effects act as a warning that overdose is being approached.

Myasthenic crisis has been successfully treated with tubocurarine and artificial respiration, to "rest" the motor endplate, in a few cases but this is an experimental remedy for a desperate situation.

The very potent long-acting anticholinesterase drugs such as dyflos are unsuitable for use in myasthenia gravis as they are too difficult to control.

---

* Disabilities and How to Live with Them (1952). London, Lancet.

† Small pupils and sweating are characteristic of a cholinergic crisis.

The Principal Uses of Choline Drugs

These may be summarised:—

1. To stimulate a reluctant bowel or bladder, *e.g.* after surgery (carbachol) or ganglion-blocking agents (neostigmine).

2. In the eye to constrict the pupil, make the ciliary muscle contract and reduce intra-ocular pressure (physostigmine, pilocarpine).

3. Anticholinesterases (neostigmine) as antidotes to those neuromuscular blocking agents (*e.g.* curare, gallamine), which act by competition, and in myasthenia gravis.

4. Rarely in tachycardias (methacholine).

DRUGS WHICH OPPOSE ACETYLCHOLINE

These drugs may be divided into three groups:—

1. Drugs which act principally at post-ganglionic cholinergic (parasympathetic) nerve endings. Atropine and related drugs or anticholine drugs, see below.

2. Ganglion-blocking agents, see p. 270.

3. Neuromuscular blocking agents, see p. 133.

It is not known why drugs oppose acetylcholine more at some sites than at others. The above groups are not perfectly separate for both curare and atropine have weak ganglion-blocking effects.

ATROPINE AND RELATED DRUGS—"ANTICHOLINE" DRUGS

Atropine and related drugs block the effect of acetylcholine principally at post-ganglionic cholinergic (parasympathetic) endings, site 2 on the diagram on p. 228. They also block the direct vasodilator effect of acetylcholine on the blood vessels and in the central nervous system. Some drugs of this group have a blocking effect at autonomic ganglia also, but none block the neuromuscular junction.

The actions of atropine will first be described. Other drugs will be dealt with chiefly in how they differ from atropine. Many anticholine drugs have a wide variety of other actions, *e.g.* antihistaminic, but find a place in therapeutics as anticholine agents.

Atropine

Atropine is an alkaloid from the plant Atropa belladonna named after the senior of the three legendary Fates, Atropos, who cuts with shears the web of life spun and woven by her sisters Clotho and Lachesis (there is a minor synthetic atropine-like drug called lachesine). The term belladonna refers to the female practice of using an extract of the plant to dilate the pupils, which was fashionable long ago. The plant has had wide and successful use throughout history as a poison.

Atropine acts by competing for the same drug receptors as acetylcholine, blocking them, and thus rendering the acetylcholine ineffectual.

In general the peripheral effects of atropine are inhibitory but there is commonly a transient phase of stimulation before the inhibition occurs and in the case of the heart this can have clinical importance (p. 138). Atropine also blocks the effects of injected choline drugs peripherally and on the central nervous system. The clinically important actions of atropine are listed below; they are mostly the opposite of the stimulant effects on the parasympathetic system produced by choline drugs (pp. 229–230).

Atropine at Parasympathetic Post-ganglionic Nerve Endings

EXOCRINE GLANDS. All secretions except milk are diminished, and dry mouth is a common side-effect. Gastric secretion is only significantly altered with high doses which are likely to cause dry mouth. The nervous phase of gastric secretion is affected more than the chemical phase, volume, acid and enzyme secretion being reduced. Sweating (sympathetic nerve supply, but cholinergic) is inhibited. Bronchial secretions are reduced and may become viscid, which can be a disadvantage, as removal of secretion by cough and ciliary action is rendered less effective.

SMOOTH MUSCLE is relaxed. In the gastro-intestinal tract there is reduction of tone and peristalsis. Muscle spasm of the intestinal and urinary tracts induced by morphine is reduced, but such spasm in the biliary tract is not. Atropine relaxes bronchial muscle and it slows micturition, although seldom enough for the patient to notice any change. Urinary retention occurs very rarely.

In the eye mydriasis occurs, with a further rise in intra-ocular pressure if it is already raised. This is traditionally said to be due to the dilated iris blocking drainage of the intra-ocular fluids from the angle of the anterior chamber, or it may be due to arteriolar dilatation without capillary dilatation causing a rise in pressure at the point where the fluids drain from the eye. An attack of glaucoma may be induced. There is no significant effect on pressure in normal eyes. The ciliary muscle is relaxed and so the eye is accommodated for distant vision. After atropinisation normal pupillary reflexes may not be regained for two weeks, or even more. Atropine is a cause of unequal sized pupils.

THE CARDIOVASCULAR SYSTEM. Atropine reduces vagal tone, thus increasing the heart rate, and enhancing conduction in the bundle of His, effects which are less marked in the elderly in whom vagal tone is low. Transient initial vagal stimulation, probably in the central nervous system, may be of clinical importance when atropine is given with neostigmine, as when the latter is used to antagonise curare-like drugs. It is generally recommended that the atropine be given a few minutes before the neostigmine to avoid the summation of the two drugs on the vagus. Atropine has no significant effect on peripheral blood vessels in therapeutic doses, but in poisoning there is marked vasodilatation.

Atropine on the Central Nervous System

The central nervous system is stimulated by atropine. The respiratory stimulation counteracts morphine depression in anæsthetic premedication, but the effect is not strong enough for the drug to be useful in cases of morphine poisoning.

Restlessness and mental excitement occur with large doses and even mania, delirium and hallucinations. Hyperthermia occurs, made worse by the concurrent prevention of sweating.

Atropine is useful against both tremor and rigidity of Parkinsonism. The mode of action is unknown. It abates motion sickness.

Antagonism to Choline Drugs

Atropine opposes the effects of all choline drugs on the central nervous system, at post-ganglionic cholinergic synapses and on the peripheral blood vessels. It does not oppose cholinergic effects at the neuromuscular junction or significantly at the autonomic ganglia (*i.e.* atropine opposes the muscarine but not the nicotine-like effects of acetylcholine).

Absorption, Metabolism and Dosage of Atropine

Absorption occurs well from the alimentary tract and atropine may be injected by the usual routes. It is slightly absorbed from mucous membranes, but the occasional cases of atropine poisoning following use of eye drops are probably due to the solution running down the lachrymal ducts into the nose and being swallowed. This mishap seems to occur most often in children.

Atropine is mostly destroyed in the liver but some is excreted unchanged by the kidney. Some tolerance occurs. For chronic use it is usually given three times a day.

The usual dose of the sulphate is 0·5 to 1 mg. s.c., i.v. or by mouth. For chronic use in Parkinsonism or peptic ulcer it is usually necessary to find the maximum tolerated dose (by increasing the dose until undesirable effects occur and then reducing it slightly) to obtain any useful therapeutic result.

Toxic Effects of Atropine

Atropine poisoning presents with the more obvious peripheral effects, dry mouth (with dysphagia), mydriasis, blurred vision, hot dry skin, and, in addition, hyperpyrexia, restlessness, anxiety, excitement, hallucinations, delirium, mania and later cerebral depression and coma—or as it has been described with characteristic American verbal felicity, "hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a hen" (2). It may occur in children who have eaten berries of any of the solanaceous plants, *e.g.* deadly nightshade and henbane. When the diagnosis is doubtful it is said to be worth putting a drop of the patient's urine in *one* eye of a cat (the rabbit is less sensitive). Mydriasis, if it results, confirms the diagnosis, but absence of effect does not negate it. The treatment of atropine poisoning is on general principles as there is no specific antidote. Use of choline drugs may reduce the peripheral effects which are not the cause of death, but the stimulant central nervous system effects cannot be antagonised other than by cautious use of depressants such as barbiturates or paraldehyde which, in the later stages of atropine poisoning, will summate dangerously with the terminal cerebral depressant effect of the poison, so that they are best avoided if possible.

Other Anticholine Drugs

In the accounts which follow, the principal peripheral atropine-like effects of the drugs may be assumed. The points in which they differ from atropine are the main topics.

Hyoscyamine is less active in the central nervous system. Atropine is racemic hyoscyamine, "hyoscyamine" is the lævo form; the dextro form is only feebly active. The dose of hyoscyamine hydrobromide is 0·3 to 0·6 mg. Atropine is more stable chemically and so is preferred.

Hyoscine Hydrobromide (scopolamine hydrobromide) is chemically related to atropine. It differs chiefly in being a central nervous system depressant although it may sometimes cause excitement. It also stimulates respiration like atropine. Elderly patients are often confused by hyoscine and so it is avoided in their anæsthetic premedication. Mydriasis is briefer than with atropine. The dose is 0·3 to 0·6 mg. Genoscopolamine is similar to hyoscine.

Atropine Methonitrate blocks autonomic ganglia as well as having strong peripheral effects, especially on the intestinal tract and salivary secretion. It is chiefly used in the conservative treatment of congenital hypertrophic pyloric stenosis, 0·12 to 0·2 ml. (from a graduated dropper) of 0·6% alcoholic solution being given orally six times a day before meals, or as lamellæ. The maximum tolerated dose may be needed. Extremely, perhaps excessively, optimistic claims for its efficacy in this disease have been made. Atropine methonitrate is also advocated as an antitussive in whooping cough on slender evidence.

Hyoscyamus, Stramonium and Belladonna are crude plant preparations containing hyoscyamine, hyoscine and atropine in varying proportions. At one time Bulgarian belladonna had a high reputation as a remedy in Parkinsonism. It was taken in white wine "after the first sleep" and was part of a system of "cure" which included bathing in water warmed by the sun and sleeping only on the right side. This routine naturally had a marked, but only temporary, success. Bulgarian belladonna was soon shown not to be superior to other forms. The dose of Dry Extract of Belladonna, B.P., of Stramonium, B.P., or of Hyoscyamus, B.P., is 15 to 60 mg.; that of Tincture of Belladonna, B.P., or of Stramonium, B.P., is 0·6 to 2 ml.; that of Tincture of Hyoscyamus, B.P. is 2 to 4 ml.

Hyoscine Methobromide (Pamine Bromide) is longer acting than hyoscine and has negligible central nervous system effects. The dose is 2·5 to 5 mg. orally, three times a day. 0·25 to 1 mg. may be injected s.c. or i.m.

Hyoscine Butylbromide (Buscopan) is similar to the methobromide. The dose is 10 to 20 mg. orally three or four times a day, 20 mg. may be given s.c., i.m. or i.v.

Homatropine is used almost solely for its ocular effects (2% of the hydrobromide as eye drops). Its action is shorter than atropine and therefore less likely to cause serious rise in the intra-ocular pressure, and so it is preferred when the pupils are to be dilated to enable the optic fundus to be seen. Its effects wear off in a day or two. Complete paralysis of accommodation cannot always be obtained unless repeated instillations are made every 15 minutes for one to two hours. It is especially unreliable in children, in whom atropine is preferred. The pupillary dilatation may be reversed by physostigmine eye-drops. Derivatives are available for systemic use but offer no important advantages.

Propantheline (Pro-Banthine) is perhaps the best known of a large number of synthetic anticholine drugs which have achieved considerable popularity, especially in the treatment of peptic ulcer. It has marked peripheral atropine-like and weak ganglion-blocking actions, so that, although it can interfere with all autonomic functions its effects are most marked on the parasympathetic division. At *very* high doses it has a curare-like effect at the neuromuscular junction, so it has been shown to be capable of antagonising acetylcholine at all peripheral cholinergic nerve endings. The side-effects are what might be expected, dry mouth, blurred vision, constipation and difficult micturition. Postural hypotension and impotence might occur. Side-effects however are not very common and the drug is relatively selective for the alimentary tract, reducing secretion and motility. The maximum tolerated dose is generally needed and this varies from 30 to 120 mg. of the bromide four times a day. It is usual to begin with 15 mg. doses.

Many drugs similar to propantheline have been made available because any really effective and selective parasympathetic-blocking agent is likely to find considerable use in treatment of peptic ulcer. It would be profitless as well as tedious to describe each drug and to enumerate the claims made for it, and so only some of the names will be given here for identification of the type of drug: dicyclomine (Merbentyl), diphemanil (Diphenatil), methantheline (Banthine), oxyphenonium (Antrenyl), penthienate (Monodral), tricyclamol (Lergine, Elorine).

Dibutoline, eucatropine and lachesine are used as mydriatics. Other drugs with anticholine effects are described under the drug therapy of Parkinsonism.

Uses of Anticholine Drugs

The clinical uses of anticholine drugs are legion. For their actions in the central nervous system some (atropine, hyoscine, and numerous synthetic drugs) are used against the rigidity and tremor of Parkinsonism in which disease doses higher than the usual therapeutic amounts are often needed and tolerated. They are used as anti-emetics (principally hyoscine) and as sedatives (hyoscine) in delirium or mania, in obstetrics and in anæsthetic premedication. For their peripheral action they (atropine, homatropine, hyoscine) are used in ophthalmology to dilate the pupil and to paralyse ocular accommodation, but they have the disadvantage of increasing intra-ocular pressure. In the respiratory tract they (atropine, belladonna, stramonium) are used as bronchodilators for which purpose they are not particularly effective, and also to reduce secretions.

For their actions on the alimentary tract a wide range, but chiefly belladonna, atropine and propantheline, are used against gastric secretion and muscle spasm and hypermotility throughout the tract. They are used in ulcerative colitis, and against colic, which is pain due to spasm of smooth muscle, and to prevent morphine-induced muscle spasm when that analgesic is used against colic.

In the urinary tract the drugs (atropine, belladonna, hyoscyamus) are used against muscle spasm accompanying infection in cystitis and against colic. They have been tried in nocturnal enuresis and dysmenorrhœa with little or no benefit.

Hyperhidrosis may be relieved by propantheline. In disorders of the cardiovascular system anticholine drugs are seldom very useful. They may be useful in attacks of cardiac arrest due to hypersensitive carotid sinus reflexes and occasionally in heart-block (atropine), but the initial vagal stimulation is a disadvantage.

In choline-drug poisoning atropine is an important antidote against both central nervous, parasympathomimetic and vasodilator effects. It is also used to block autonomic effects when choline drugs, such as neostigmine, are used for their effect on the neuromuscular junction in myasthenia gravis. This group of drugs is sometimes contra-indicated in elderly people, because of the risk of inducing glaucoma, or urinary retention in the presence of prostatic hypertrophy. In organic pyloric stenosis these drugs may prevent gastric emptying by reducing peristalsis and they may also make œsophageal achalasia worse, but they are useful in infantile pyloric stenosis.

DRUG TREATMENT OF PARKINSONISM

The symptoms in Parkinsonism that require alleviation are tremor, rigidity and akinesia. Drugs form only part of the treatment however, psychotherapy, physiotherapy and surgery all having their places.

The site of therapeutic action of antiparkinsonian drugs may be the brain stem reticular formation for, although the pathological lesions are elsewhere, there is evidence that the disordered activity may be relayed through, or be due to a release from control of, the reticular formation. The synapses of the reticular formation seem to be cholinergic for they are activated by acetylcholine and anticholinesterases in animal experiments and these effects can be prevented by atropine. Nearly all the drugs of use in Parkinsonism are anticholine drugs, but the treatment is still largely empirical and follows from the clinical observation in 1901 that drugs of the belladonna group are beneficial.

Numerous attempts to devise laboratory experiments to screen substances for their therapeutic effect in Parkinsonism have been made; none has yet resulted in improved therapy, presumably because they do not in fact parallel the human disease. Clinical improvement due to antiparkinsonian drugs is not great, 25% at most. There are innumerable drugs from which to choose which, in this, as in most conditions for which there is a multiplicity of remedies, means that none is dramatically effective.

Claims that this or that drug is more effective either against rigidity or against tremor rest on an insecure basis, but these are the symptoms chiefly affected. Akinesia is seldom or never benefitted. There is very great variability between patients in their response to drugs and it is quite impossible to know in advance what drug or combination of drugs will suit any one patient. It is therefore necessary to try drug after drug, usually taking the dose slowly up to the maximum the patient can tolerate, until the optimum is found. As many as ten combinations may have to be tried. It is very tedious, but the preservation of physical independence is worth a lot.

An ineffective drug may be withdrawn totally at once, but an effective or partially effective drug should only be withdrawn gradually as the next drug is commenced, or the patient may relapse and may even become so rigid that he cannot eat.

A hindrance to the development of rational therapy is the great variability of the symptoms in any one patient from day to day, so that accurate measurement of drug effects is difficult. However, by using a battery of tests, grip strength, finger-thumb proximation rate, circle drawing, handwriting, time to walk 10 metres and others, it has been possible to obtain some quantitative estimate of the value of different drugs (8). Unfortunately many studies are still carried out on a basis of clinical impressions and it is doubtful whether any two physicians would agree on the best combinations of drugs.

Until 1947 the belladonna group of natural alkaloids was the mainstay of therapy. Now synthetic drugs are dominant. Drugs which have

DATA ON SOME SYNTHETIC ANTIPARKINSONIAN DRUGS

Name	*Principal type of drug action*	*Each oral dose (doses/day in brackets)*	*Remarks*
ethopropazine (Lysivane)	anticholine	50–125 mg. (2–5)	Chemically related to chlorpromazine. Occasionally causes muscle cramps.
benzhexol (Artane, Pipanol)	anticholine	2–12 mg. (3)	May cause excitement and mental confusion if dose increased too rapidly.
orphenadrine (Disipal)	anticholine antihistaminic	50-100 mg. (4)	Chemically closely related to diphenhydramine (Benadryl) but less soporific.
procyclidine (Kemadrin)	anticholine antihistaminic	2·5–10 mg. (3–4)	High doses can cause mental confusion
benztropine (Cogentin)	anticholine antihistaminic	0·5–2 mg. (1–3)	Recommended that a drug with cerebral-stimulant effect (benzhexol, cycrimine, amphetamine) be combined.
cycrimine (Pagitane)	anticholine	2·5–10 mg. (3–4)	Chemically similar to benzhexol. May cause restlessness and excitement especially in the aged.
diethazine (Diparcol)	anticholine	50–500 mg. (3)	May be given [illegible] for urgent relief of rigidity or oculogyric crises. Agranulocytosis occurs rarely.
caramiphen (Parpanit)	anticholine	20–50 mg. (5)	Short-acting. Not very useful.

The doses are those of the commonly used salt.

been especially recommended in Parkinsonism are ethopropazine (Lysivane), phenindamine (Thephorin), benzhexol (Artane), orphenadrine (Disipal), procyclidine (Kemadrin), benztropine (Cogentin), cycrimine (Pagitane). Others which may suit individual patients very well are diphenhydramine (Benadryl), amphetamine, the belladonna group (atropine, hyoscine), promethazine (Phenergan), diethazine (Diparcol), caramiphen (Parpanit). Further details of some of these are given in the table. All antihistaminics with atropine-like effects can be tried. Chlorpromazine and similar drugs are of occasional benefit, although in large doses they may cause a Parkinsonian syndrome, as may reserpine. The latter drug is of no benefit in this disease.

In the face of this multitude of drugs it is impossible to be dogmatic on initial therapy for a patient. A start may be made by giving, say, ethopropazine 50 mg. twice a day and increasing the dose twice a week by increasing the frequency of administration up to four or five times a day, and then increasing the amount in each dose until the patient begins to get side-effects, often at about 500 mg. a day. The dose is then slightly reduced. When the maximum benefit has been obtained with ethopropazine, or the drug withdrawn because no benefit has accrued, benzhexol (2 mg. three times a day) may be given and increased every five to seven days in the same way, the maximum tolerated dose usually being about 15 to 20 mg. a day. After this orphenadrine is worth trying. If it is desired to use the belladonna group of drugs, a start may be made with hyoscine 0·3 mg. three times a day and this increased twice a week up to the maximum tolerated dose which may be in the region of 1 mg. A convenient method is to use a solution, which enables the patient more easily to adjust his own dosage. An example would be to prescribe a 0·5% solution of atropine sulphate and instruct the patient to take three drops thrice daily and to increase each dose by one drop twice a week until he develops dry mouth or blurred vision. He then reverts to a dose just less than that producing side-effects. A standard dropper must be used. Such a solution loses potency and should be renewed every month. When the ideal dose is found, tablets may be substituted, as they are more conveniently portable. A patient who is not benefitted by atropine may be helped by hyoscine and vice versa.

More than three drugs are seldom needed. Amphetamine or pipradrol may be useful; they probably modify the symptoms directly as well as alleviating mental depression or sedation due to other drugs.

Parkinsonian patients often tolerate very large doses of drugs and tolerance to side-effects may occur. Drugs are best given after food to achieve an even effect. Oculogyric crises may require ethopropazine, 250 mg., i.m. If sialorrhœa is troublesome a drug of the belladonna group will stop it. Excessive dryness of the mouth with these drugs can sometimes be usefully countered by a small dose of pilocarpine or by sucking acid sweets, if the dose of the antiparkinsonian drug cannot be reduced without loss of benefit.

Drugs which are mentioned above and not included in the table are described in other parts of the book. All with anticholine effects may aggravate glaucoma.

Other involuntary movements (chorea, tics, torsion spasm) are not consistently improved by any drugs.

Guide to Further Reading

On Choline Drugs

(*1*) Harris, M. M., and Pacella, B. L. (1943). Convulsant shock treatment of patients with mental disease by intravenous injection of acetylcholine. *Arch. Neurol. Psychiat.* (Chicago), **50**, 304.

(*2*) Cohen, L. H., Thale, N. J., and Tissenbaum, M. J. (1944). Acetylcholine treatment of schizophrenia. *Arch. Neurol. Psychiat* (Chicago), **51**, 171.

(*3*) Hawkings, J. R., and Tibbetts, R. W. (1956). *J. ment. Sci.*, **102**:—

a. Intravenous acetylcholine therapy in neurosis. A controlled trial, page 43.

b. Carbon dioxide inhalation therapy in neurosis. A controlled clinical trial, page 52.

c. The placebo response, page 60.

(*4*) Grob, D., Johns, R. J., and Harvey, A. M. (1956). Studies in neuromuscular function. *Bull. Johns Hopk. Hosp.*, **99**, 115 to 181.

(*5*) Symposium on myasthenia gravis (1955). *Amer. J. Med.*, **19**, 658.

(*6*) Paton, W. D. M. (1958). *In* Modern Trends in Anæsthesia. Ed F. T. Evans and T. C. Gray. London: Butterworth.

(*7*) Schwab, R. S. (1960). The pharmacologic basis of the treatment of myasthenia gravis. *Clin. Pharmacol. and Therap.*, **1**, 319.

On Anticholine Drugs

(*1*) Cullumbine, H., McKee, W. H. E., and Creasey, N. H. (1955) The effects of atropine sulphate upon healthy male subjects. *Quart. J. exp. Physiol.*, **40**, 309.

(*2*) Morton, H. G., and Durham, N. C. (1939). Atropine intoxication. *J. Pediat.*, **14**, 755.

(*3*) Kay, A. W., and Smith, A. N. (1956). The action of atropine and hexamethonium in combination on basal gastric secretion. *Brit. J. Pharmacol.*, **11**, 231.

(*4*) Sun, D. C. H., Shay, H., and Ciminera, J. L. (1955) Relative effectiveness of anticholinergic drugs on basal gastric secretion. *J. Amer. med. Ass.*, **158**, 713.

(*5*) Grant, W. M. (1955). Physiological and pharmacological influences upon intraocular pressure. *Pharmacol. Rev.*, **7**, 143.

(*6*) Randall, W. C., and Kimura, K. K. (1955). The pharmacology of sweating. *Pharmacol. Rev.*, **7**, 365.

(*7*) Williams, E. M. V. (1954) The mode of action of drugs upon intestinal motility. *Pharmacol. Rev.*, **6**, 159.

(*8*) Schwab, R. S., and Prichard, J. S. (1951). An assessment of therapy in Parkinson's disease. *Arch. Neurol. Psychiat.* (Chicago), **65**, 489.

Chapter 14

SYMPATHOMIMETICS

As their name implies the sympathomimetic drugs mimic the effects of stimulation of the sympathetic division of the autonomic nervous system. They include substances which occur naturally in the body:-

(1) Adrenaline (epinephrine) which is the main hormone of the adrenal medulla but which is also produced in small amounts at adrenergic nerve endings.

(2) Noradrenaline (norepinephrine, levarterenol, arterenol) which is the main transmitter at post-ganglionic sympathetic adrenergic nerve endings, but which is also present in small amounts in the adrenal medulla.

(3) Isoprenaline (isoproterenol, isopropylnoradrenaline) which is present in tiny amounts in the adrenal medulla.

A very large number of related compounds with sympathomimetic effects have been synthesised, but only a few have earned a place in therapeutics. Ephedrine was originally found in a Chinese plant but is now synthesised. The amphetamine group of drugs are sympathomimetic but are also important for their effects on the central nervous system.

History

Sir Henry Dale has told of the discovery of the hypertensive effect of adrenaline: "Dr. Oliver . . . was a physician in practice. . . . He appears to have used his family in his experiments, and a young son was the subject of a series, in which Dr. Oliver measured the diameter of the radial artery and observed the effect upon it of injecting extracts of various animal glands under the skin. We may picture Professor Schafer . . . finishing an experiment . . . in which he was recording the arterial pressure of an anæsthetised dog. To him enters Dr. Oliver, with the story of the experiments, and, in particular, with the statement that injection under the skin of a glycerine extract from the calf's suprarenal gland was followed by a definite narrowing of the radial artery. Professor Schafer is said to have been entirely sceptical, and to have attributed the observation to self-delusion. . . . Dr. Oliver, however, is persistent . . . so Professor Schafer makes the injection, expecting a triumphant demonstration of nothing, and finds himself standing 'like some watcher of the skies, when a new planet swims into his ken', watching the mercury rise in the manometer with amazing rapidity and to an astounding height. . . ."*

---

* DALE, H. (1938). *Edin. med. J.*, **45**, 461.

This discovery led eventually to the isolation and synthesis of adrenaline in the early 1900's. Many related compounds were examined and in 1910, Barger and Dale introduced the term sympathomimetic and also pointed out that noradrenaline mimicked the action of the sympathetic nervous system more closely than did adrenaline. Nevertheless adrenaline was generally thought to be the sympathetic mediator for the next 35 years, partly because noradrenaline was not known to be present in the body, and partly because many of the preparations of "adrenaline" available did in fact contain a substantial amount of noradrenaline. Clarification of the situation had to wait until accurate methods both of identifying adrenaline and noradrenaline and of estimating them separately were developed.

Mode of Action of Sympathomimetic Drugs

Adrenaline and noradrenaline act directly on the effector cell-receptors and are chemical transmitters of the nervous impulse comparable with acetylcholine. Most of the other members of the group act similarly, but some, particularly ephedrine, may act partly by causing a release of adrenaline or noradrenaline stored in the end-organ. Many of these drugs are racemic compounds and one form is often much more active; for instance lævo-noradrenaline, the commonly used form, is at least 50 times as active as the dextro form.

Effects of Adrenaline, Noradrenaline, Isoprenaline (see Table, p. 251)

These depend on the dose, for instance adrenaline ordinarily dilates muscle blood vessels (mainly arterioles, but capillaries and veins also) but in very large doses constricts them. The actions described in the table are those of doses used in therapeutics or of amounts ordinarily liberated in the body. The end results are often complex and unpredictable, partly because of the variability of homeostatic responses and partly because what is observed (*e.g.* a change in blood pressure) is the result of many factors (*e.g.* vasodilatation in some areas, vasoconstriction in others, and cardiac stimulation).

Side-effects of Sympathomimetic Drugs

Side-effects may be deduced from the physiological effects. Tissue necrosis due to intense vasoconstriction around injection sites is particularly prone to occur as a result of leakage from i.v. infusions. The effects on the heart are usually unwanted and are the commonest cause of deaths due to these drugs (ventricular arrhythmias), and sympathomimetic drugs should obviously be used with great caution in patients with heart disease liable to arrhythmias. They are particularly likely to cause cardiac arrhythmias if used in patients under chloroform, trichlorethylene or cyclopropane anæsthesia. The effect of the sympathomimetic drugs on the pregnant

The Principal Effects of Noradrenaline, Adrenaline and Isoprenaline

Effect on	*Noradrenaline*	*Adrenaline*	*Isoprenaline*
Heart: (*a*) rate	slowed (reflexly due to B.P. rise)	increased (direct action)	increased (direct action)
(*b*) force of mycardial contraction	little effect	increased (direct action) "palpitations" due to $a + b$	increased (direct action) "palpitations" due to $a + b$
(*c*) cardiac output	insignificant	increased	increased
(*d*) excitability	increased	much increased	much increased
Blood pressure:			
(*a*) systolic	rises	rises (due to *b* and *c* above)	little change, or may fall
(*b*) diastolic	rises	falls (due to *a* below)	falls
Vascular beds in:			
(*a*) muscle	constricted	dilated	dilated
(*b*) skin & viscera	constricted	constricted	dilated
(*c*) heart	? dilated	dilated	dilated
total peripheral resistance	increased	decreased	decreased
Metabolism:			
O_2 consumption, liberation of glucose	insignificant	increased	none
Central nervous system	insignificant	stimulation: feelings of fear and anxiety, respiration increased, tremor	stimulation
Smooth muscle:			
(*a*) bronchi	little effect	relaxed	relaxed
(*b*) intestine and bladder	relaxed	relaxed	relaxed
(*c*) sphincters	constricted	constricted	constricted
(*d*) uterus	contracted	unpredictable	?
Capillary permeability	little effect	reduced	?

It will be seen that the actions of isopropylnoradrenaline (isoprenaline) are more akin to those of adrenaline than to noradrenaline.

uterus is very variable and difficult to predict, but serious fœtal distress can occur, due to reduced placental blood flow as a result of contraction of the uterine muscle and arterial constriction.

Metabolism of Sympathomimetic Drugs

Noradrenaline is probably the precursor of adrenaline and of isoprenaline in the body. The way in which adrenaline, noradrenaline and isoprenaline are destroyed is not known, but it has been suggested that the enzyme mono-amine oxidase has a comparable role to that of cholinesterase at cholinergic nerve endings. However, completely and irreversibly blocking mono-amine oxidase with iproniazid does not greatly alter the response to sympathomimetic drugs and there are a number of other objections to this theory (*1*). Only about 2% of circulating adrenaline, noradrenaline or isoprenaline is excreted unchanged in the urine, but this is enough to be useful in the diagnosis of phæochromocytoma. The response to sympathomimetic drugs (except ephedrine) is increased for a time after sympathectomy. Adrenaline and noradrenaline are not given by mouth because most is destroyed in the alimentary tract and what is absorbed is metabolised by the liver, so that insignificant amounts enter the general circulation. Ephedrine and the amphetamines however are not metabolised so fast by the liver, and so are effective given by mouth. Isoprenaline is rapidly metabolised by the liver, but is quite well absorbed from mucous membranes, partly because it does not have the vasoconstrictor effects of other sympathomimetics; it is often given as tablets to be dissolved under the tongue. The free bases of the sympathomimetic drugs are relatively insoluble and so they are given as salts. Most are readily oxidised to inactive compounds and so reducing agents are always added to solutions as preservatives (see footnote, p. 258).

Adrenaline

Adrenaline is mainly used as a bronchodilator and in the treatment of hypersensitivity reactions (p. 445). It is not given intravenously, except as a last resort, because of the risk of cardiac arrhythmias, but is given by subcutaneous injection with precautions to ensure that the needle is not in a vein. Local constriction of the vessels is produced, which slows absorption and so prolongs and smooths out the effects. Nevertheless it should be given in small repeated doses, 0·1 ml. a minute of 1 : 1,000 solution (Adrenaline Injection, B.P.) until either the desired response occurs or toxic effects appear, or the maximum safe dose of about 0·5 ml. over 15 minutes has been given. The vasoconstrictor effect is also made use of when adrenaline (1 : 50,000 or weaker) is added to local anaesthetics to prolong their effects (noradrenaline at the same strength is as effective and may be safer). A much stronger solution of adrenaline (1%) is often used by oral inhalation in bronchial asthma and by nasal inhalation in allergic rhinitis. Enough can be absorbed by these routes to have significant systemic effects. The main action in asthma is to relax the bronchial muscle, but the airway is also improved by vasoconstriction and reduction of capillary permeability which reduce the swelling of the bronchial mucous membranes. Intracardiac injections of adrenaline are used in cardiac arrest for their stimulating effect on the heart; even though ventricular fibrillation may be provoked it can sometimes be converted to normal rhythm with an electrical defibrillator. The metabolic effects of adrenaline are now seldom used in therapeutics, but it used to be given in insulin hypoglycæmia to mobilise liver glycogen. Thyrotoxic patients are said to be unusually sensitive to adrenaline and asthmatic patients sometimes become tolerant to it; habituation though not addiction also occurs.

Noradrenaline

The main effect of noradrenaline is to raise the blood pressure by constricting the arterioles and this is its principal use in therapeutics. Noradrenaline is always given by intravenous infusion to obtain a gradual sustained response, the effect of a single i.v. injection would only last a minute or so. It is available in ampoules of solution containing 1 mg./ml. of base and these are diluted (usually 4 ml./litre) in whatever fluid for i.v. infusion seems suitable, the usual dose range is 2 to 4 μg/minute (approximately 15 to 30 drops/minute) but the rate is always adjusted according to the response. Blood pressures must be taken at not less than 5-minute intervals, and more frequently at the beginning of the infusion. Gangrene of the extremities may follow prolonged infusions and necrotic ulceration of large areas round the infusion vein can occur, for even if the needle does not slip out of the vein, some will leak out. The risk of gangrene can be minimised by using a large vein and rapid flow of dilute solution for the shortest possible time. If an extravasation is detected, the adrenergic blocking agent phentolamine should be injected into the area. If an infusion of noradrenaline is given for many hours some blood vessels may cease to respond, and the blood pressure may fall, so that the dose has to be increased even though some vessels at the periphery may be so constricted that gangrene begins. Noradrenaline infusions should be stopped gradually because their sudden cessation may be followed by a catastrophic fall in the blood pressure. Many explanations have been put forward both for this and for the development of tolerance, but none are certainly established. The difficulties and dangers, including cardiac arrhythmias, of noradrenaline infusions are undoubted, and the benefits obtained from them in, for instance, hypotensive states (p. 258) may be questioned; they should be avoided whenever possible. The maintenance of the blood pressure immediately following the removal of a phæochromocytoma is probably the most rational, though rare, use of noradrenaline infusions. The fact that vasoconstriction is more prominent than any of its other effects would seem to make it the ideal sympathomimetic for use with local anæsthetics (1:50,000 or weaker), and for surface use (1:1,000) to stop nose bleeds and bleeding tooth sockets; however, adrenaline is traditionally used for these purposes.

Isoprenaline (isoproterenol)

Isoprenaline relaxes smooth muscle, including that of the blood vessels, has negligible metabolic or vasoconstrictor effects, but has a vigorous stimulant effect on the heart. This latter is its main disadvantage in the treatment of bronchial asthma and precludes injection. However, isoprenaline is sometimes used in complete heart block. It is given as tablets of the sulphate to be dissolved under the tongue (10 to 20 mg.), and repeated as necessary. In asthma an oral spray (1%) or aerosol are often used and may cause less palpitations and tachycardia than the sublingual tablets.

Ethylnoradrenaline (Butanefrine) has similar actions to isoprenaline, but has less effect on the heart and so may be worth trying in asthma if the latter causes troublesome palpitations. A 2% solution is used for oral inhalation and 2 mg. may be given s.c. or i.m.

Ephedrine

Ephedrine is chemically similar to adrenaline and has many similar pharmacological effects; its mode of action is discussed on p. 250, but it has a relatively greater stimulant effect on the central nervous system to produce alertness, anxiety, insomnia, tremor and nausea, although asthmatic children may even be sleepy when taking it. It has sometimes been used for its effects on the nervous system, but better drugs with less systemic effects are available. In practice central effects limit its use as a sympathomimetic.

Ephedrine is well absorbed when given by mouth and unlike most other sympathomimetics is not destroyed by the liver; it is largely excreted unchanged by the kidney. It is usually given by mouth but can be injected. On a weight basis it is only about 1/250th as active as adrenaline, but this, of course, is of no particular importance since the usual 15 or 30 mg. tablets are not inconveniently bulky. It differs from adrenaline principally in that its effects come on more slowly and last longer. Tachyphylaxis occurs, and this means that ephedrine is not much use for raising the blood pressure. Its main place in therapeutics is as a bronchodilator in mild chronic asthma (30 to 75 mg. of the hydrochloride orally three to four times a day or as a 1% oral spray); a barbiturate may be needed to counter the central effects. Tolerance sometimes develops, but replacing the ephedrine for a few days with another sympathomimetic usually restores sensitivity. Ephedrine is sometimes used (8 to 30 mg. three or four times a day) to increase conduction in the bundle of His in complete heart-block. Its action on the bladder (constriction of the sphincter, relaxation of the detrusor) may be inconvenient, especially in elderly men with prostatism. It is sometimes tried in the treatment of enuresis (60 to 120 mg. at bedtime) where its effect in reducing the depth of sleep is probably more important than its action on the bladder. 1% drops are used to induce vasoconstriction in swollen nasal mucous membrane. It is a mydriatic, said to be effective in light-, but not in dark-coloured eyes (*3*), but it is not much used for this purpose. Ephedrine may have a beneficial action on the muscular weakness of myasthenia gravis by enhancing neuromuscular transmission.

Amphetamine (Benzedrine) (see also p. 207)

Amphetamine is seldom used for its peripheral effects, which are similar to those of ephedrine, but usually for its effects on the central nervous system on which it is relatively more active. The solid is volatile and used to be available, as the Benzedrine Inhaler, for nasal congestion, but addicts found this such a useful source (*8*) that the manufacturers substituted instead propylhexedrine (Benzedrex) which is as good a decongestant but which has virtually no central nervous system effects.

Methylamphetamine (Methedrine) is sometimes used to raise the blood pressure (10 to 30 mg. of the hydrochloride i.v. or i.m.) but it has as much central stimulating effect as amphetamine and this may be undesirable.

Phenylephrine (Neosynephrine)

Phenylephrine has actions qualitatively similar to noradrenaline but has a longer duration of action, up to an hour or so, and slow i.v. injections rather than infusions are given. 0·5 mg. of the hydrochloride i.v. is the usual dose to raise the blood pressure, but 5 mg. is sometimes given s.c. It can be used as a nasal decongestant (0·5 to 1% solution) but sometimes irritates. In the doses usually given, the central nervous effects are minimal, as are the direct effects on the heart. Thus it is probably a drug of choice if a vasopressor effect is required, but many of the drugs in the table on p. 256 could be used. The oral dose for allergy is 30 to 75 mg. a day total. It is also used as a mydriatic and briefly lowers intra-ocular pressure.

Methoxyphenamine (Orthoxine) has practically no central, cardiac or vasoconstrictor effects but does dilate the bronchi and is used in chronic asthma (50 to 200 mg. of the hydrochloride four times a day).

SOME SYMPATHOMIMETIC DRUGS USED TO RELIEVE MUCOSAL CONGESTION OR TO RAISE THE BLOOD PRESSURE

Drug	*Uses*	*Dose*	*Remarks*
methoxamine (Vasoxine, Vasylox)	vasopressor nasal decongestant	5–20 mg. 0·25%	like phenylephrine
mephentermine (Mephine, Wyamine)	vasopressor nasal decongestant	10–30 mg. 0·5%	like methylamphetamine, but with less CNS effects
cyclopentamine (Clopane)	vasopressor nasal decongestant	10–25 mg. 0·5%	like ephedrine but with less CNS effects
hydroxyamphetamine (Paredrinex)	nasal decongestant mydriatic vasopressor, in complete heart-block	1% 1–3% 5–20 mg. 20–60 mg. 8-hrly. orally	little CNS effect but considerable direct action on heart
metaraminol (Aramine)	nasal decongestant vasopressor	0·25–0·5% 5–10 mg.	like phenylephrine
naphazoline (Privine)	nasal decongestant	0·05–0·1%	—
phenylpropanolamine (Propadrin)	nasal decongestant	1%	like ephedrine but sometimes used to reduce appetite (50 mg. daily)
phenylpropylmethylamine (Vonedrine)	nasal decongestant	2–3%	—
tuaminoheptane (Tuamine)	nasal decongestant	1–2%	like ephedrine
tetrahydrozoline (Tyzine, Tyzanol)	nasal decongestant	0·05–0·1%	—

The other more important members are described in the text. When these drugs are used to raise the blood pressure the lower dose may be given by slow i.v. injection, repeated as necessary, or the higher doses may be given i.m. There is little to choose between them. The doses given are those of the commonly used salts.

Nasal Decongestants

Nasal decongestants (which are vasoconstrictors) are very widely used in allergic rhinitis, colds and sinusitis, as nasal drops or as inhalants to be sniffed. All the sympathomimetic vasoconstrictors have been used for the purpose, and there is little to choose between them (see table above). Long-continued use is undesirable, because local irritation, tachyphylaxis and eventually a secondary nasal congestion due to damage of the mucosa may result. Mild hypersensitivity reactions may occur and it is worth trying a different drug if irritation develops. Prolonged use of oily drops and sprays is undesirable because they may enter the lungs and eventually cause lipoid pneumonia.

Drug Treatment of Bronchial Asthma

Drugs comprise only part of the treatment of bronchial asthma. Psychological and immunological factors are very important though difficult to alter; infection may be a precipitating cause or complication and requires appropriate chemotherapy. The responsible antigen-antibody reaction liberates pharmacologically active substances, including histamine, in the bronchial muscle and these cause the muscle to contract; the mucosa also becomes œdematous and swollen, still further reducing the airway, and the bronchial secretion is sticky and hard to dislodge. Possible lines of treatment therefore include:—

1. Prevention of the antigen-antibody reaction either by desensitisation or avoidance of the antigen, if this is known.

2. Non-specific reduction of the response to the antigen-antibody reaction by the use of adrenocortical steroids. Their general effects are such that they are only used as a last resort, but are extremely effective.

3. Drugs which specifically antagonise substances liberated in the antigen-antibody reaction. So far only the antihistaminics are available and they are virtually useless in asthma.

4. Atropine-like drugs which block the parasympathetic motor nerve endings on the bronchial muscle; these are not often very useful, and tend to thicken bronchial secretion unduly.

5. Drugs which act directly on the smooth muscle of the bronchi to relax it. This is the most important group and includes the sympathomimetic drugs such as adrenaline, isoprenaline and ephedrine, and theophylline derivatives such as aminophylline and choline theophyllinate. The efficacy of bronchodilators in asthma is enhanced by phenobarbitone.

6. Production of bronchial mucosal vasoconstriction by oral sprays. Some sympathomimetic drugs, *e.g.* adrenaline, have this action (isoprenaline has not). A very fine mist, or aerosol, is needed if the droplets are to penetrate to the smallest bronchi.

Treatment naturally varies with the severity and type of asthma but may be summarised:—

For Chronic Asthma, ephedrine, with or without choline theophyllinate, is used regularly by mouth. To abort attacks an adrenaline spray (with or without atropine in addition), or isoprenaline by spray or sublingually can be used. Suitable preparations are listed in the B.N.F. Chest infections deserve vigorous treatment. Long term therapy with adrenocortical hormones is used only in severe cases when everything else has failed (*11*).

For a Mild Acute Exacerbation, isoprenaline may be sufficient, or adrenaline. Adrenaline, either as a spray or s.c., is usually effective and patients can be taught to inject themselves if necessary.*

In Status Asthmaticus, a serious medical emergency, full doses of adrenaline or isoprenaline are tried first and then aminophylline, i.v., but if relief does not occur in a few hours there should be no hesitation in using adrenocortical steroids. Hydrocortisone, i.v., is the most rapidly acting steroid but a course of an orally active steroid, say prednisone, is started at the same time. Maximal doses are given at first and reduction in the dose begun as soon as the patient's condition permits.

Chronic Bronchitis with Bronchospasm. Treatment of the bronchospasm is similar to bronchial asthma. Aminophylline, 6-hourly, i.v., may be very effective in severe relapses. Chemotherapy may be needed.

DRUGS IN HYPOTENSIVE STATES

The term "shock" is avoided here because there can be shock with normal blood pressure and because the use of vasopressor drugs is not the most important aspect of its treatment, which may be summarised:

a. Treatment of the cause: pain, wounds, infections, adrenocortical deficiency.

b. Replacement of any fluid lost from the circulating blood; but extra fluid is dangerous when the primary fault is in the heart or pulmonary circulation.

c. Maintenance of the diastolic blood pressure.

Hypotensive States may be due to:—

Reduced cardiac output.
Reduced peripheral resistance.
A mixture of both the above.

Hypotension due to low peripheral resistance is of little importance if the patient is horizontal, for blood flow to brain, myocardium and kidneys remains adequate until the diastolic pressure falls below about 40 mm. Hg., when it is possible that the coronary blood flow suffers too. But low cardiac output is always of serious significance even though compensatory vasoconstriction maintains the blood pressure, for blood flow is reduced. It is blood flow rather than blood pressure which is of the greatest immediate importance for the function of vital organs. A reasonable blood pressure is however needed to render the blood flow independent of the effects of gravity and to provide coronary perfusion and pressure for secretion of urine. If the diastolic pressure exceeds 40 mm. Hg. there is probably little danger to the patient provided that blood flow is normal.

---

* When solutions (spray or injection) of adrenaline or isoprenaline fail to give relief, inspect them. If they are brown or not perfectly clear, they *may* have seriously lost potency.

Low blood pressure states in which blood flow to vital organs is not significantly reduced, so long as the horizontal position is maintained, occur as a result of vasovagal attacks, overdose of vasodilator drugs and in spinal anæsthesia. In all these there is arteriolar dilatation. The treatment is to keep the patient horizontal, but if the hypotension is unduly severe or prolonged the blood pressure may be restored by vasoconstrictor drugs (noradrenaline, phenylephrine, methoxamine, methylamphetamine) which can be highly effective. An excess of vasoconstriction will, of course, itself reduce blood flow.

Low blood pressure states associated with low cardiac output, and accompanied by compensatory peripheral vasoconstriction occur:

When there is a Primary Fault in the Heart (myocardial infarction) or in the pulmonary circulation (pulmonary artery embolus). It is possible to advance reasons why vasoconstrictor drugs may be useful in these conditions, but proof of therapeutic benefit is hard to get. In the case of myocardial infarction it may be contended that a higher diastolic pressure is required to perfuse the collateral circulation to the damaged area than is needed to perfuse the healthy areas, and that if this pressure is provided, muscle on the edge of the infarct that would have died may remain viable, so that the total size of the infarct will be less than it would otherwise have been.

In the case of pulmonary artery embolus, the output of the right ventricle, and so the volume of blood going to the left ventricle, is reduced and as a result the coronary blood flow to both ventricles falls. The right ventricle is therefore doing more work, against the obstructed pulmonary artery, with less oxygen supply to its muscle. If the peripheral resistance is raised by giving vasoconstrictors the diastolic pressure in the aorta will rise and the coronary flow will improve, which may benefit the overworked right ventricle.

These reasons are backed by some experimental findings in animals, but the use of vasoconstrictor drugs must be regarded as based on speculation, despite enthusiastic claims made for them.

The risk of causing cardiac arrhythmias in myocardial infarction by the use of sympathomimetic drugs is substantial, for all these drugs have some cardiac stimulant effect even though many are predominantly vasoconstrictors.

In Oligæmic States. Drugs have no place. Replacement of the lost fluid by adequate transfusion is the only appropriate treatment.

In Bacterial Toxæmia and Adrenocortical (Addisonian) Crisis. In these conditions there is dilatation of the small vessels, especially the venules, so that administration of drugs whose principal action is to constrict the arterioles cannot be expected to give benefit. Fluids infused i.v. accumulate in the dilated vessels.

Hydrocortisone in Hypotensive States

Hydrocortisone is of course essential if there is known to be adrenal cortical failure, and it is reasonable to give it in any prolonged hypotensive state. This is especially advocated in bacterial toxæmia, in which condition the prognosis is extremely bad, but there is no conclusive proof of benefit.

General

As a result of prolonged anoxia, whether due to intense vasoconstriction or to low cardiac output, it is possible that the peripheral vessels cease to respond normally to drugs and that a substantial part of any rise in blood pressure that occurs in response to sympathomimetic drugs is due to cardiac stimulation. In general it cannot be assumed that diseased tissues will always exhibit the pharmacological responses that have been demonstrated on normal tissues.

The fact that the use of drugs in most serious hypotensive states is still based on very slender evidence is shown by the fact that treatment exactly contrary to the above has been advocated since it has been shown that adrenergic blocking drugs reduce the mortality from some forms of shock in experimental animals. It has been proposed that shocked patients should be given large doses of the adrenergic blocking agent, phenoxybenzamine, and the blood pressure regulated by tilting the patient. This therapy is still experimental.

Guide to Further Reading

On Sympathomimetic Drugs

(*1*) Robson, J. M., and Keele, C. A. (1956). Noradrenaline, adrenaline and isoprenaline. *In* Recent Advances in Pharmacology, 2nd ed. London: Churchill.

(*2*) Euler, U. S. von (1956). Noradrenaline: Chemistry, Physiology, Pharmacology and Clinical Aspects. Springfield: Thomas.

(*3*) Editorial (1957). The fate of adrenaline in the body. *Brit. med. J.*, (*ii*), 1226.

(*4*) Gaddum, J. H. (1938). The alkaloid ephedrine. *Brit. med. J.*, (*i*), 713.

(*5*) Angenent, W. J., and Koelle, G. B. (1953). A possible enzymatic basis for the differential action of mydriatics on light and dark irides. *J. Physiol.*, **119**, 102.

(6) FABRICANT, N. D. (1953). Effect of progressively buffered solution of ephedrine on nasal mucosa. *J. Amer. med. Ass.*, **151**, 21.

(7) FEINBERG, S. M., and FRIEDLAENDER, S. (1945). Nasal congestion from frequent use of privine hydrochloride. *J. Amer. med. Ass.*, **128**, 1095.

(8) MONROE, R. R., and DRELL, H. J. (1947). Oral use of stimulants obtained from inhalers. *J. Amer. med. Ass.*, **135**, 909.

(9) BARCROFT, H., and KONZETT, H. (1949). On the actions of noradrenaline, adrenaline and isopropylnoradrenaline on the arterial blood pressure, heart rate and muscle blood flow in man. *J. Physiol.*, **110**, 194.

(10) BARCROFT, H., and SWAN, H. J. C. (1953). Sympathetic Control of Human Blood Vessels. London: Arnold.

(11) PHEAR, D., *et al*. (1960). Prolonged treatment with steroids in severe chronic asthma. *Lancet*, (*i*), 139.

On Drugs in Hypotensive States

(1) GREISMAN, S. E. (1959). The physiologic basis for vasopressor therapy during shock. *Ann. intern. Med.*, **50**, 1092.

Chapter 15

HYPOTENSIVE AND VASODILATOR DRUGS

THESE drugs may act at any of the following sites:—

1. **Vessel Wall Unrelated to Nerve Endings,** *e.g.* nitrites, xanthines, choline drugs and numerous drugs advocated for use in peripheral vascular disease.

2. **In Relation to Sympathetic Nerve Endings on the Blood Vessels,** *e.g.* adrenergic blocking drugs (phentolamine, phenoxybenzamine, tolazoline).

3. **Sympathetic Nerve Fibres (Post-ganglionic),** *e.g.* bretylium, guanethidine.

4. **Sympathetic Autonomic Ganglia,** *e.g.* pempidine, mecamylamine, hexamethonium.

5. **Central Nervous System,** *e.g.* reserpine, hydralazine.

6. **Afferent Nerve Endings,** *e.g.* veratrum.

7. **Blood.** The hypotensive effect of chlorothiazide may be due to its effects on blood volume, but this is by no means certain, see p. 308.

Some drugs act at more than one site (tolazoline, reserpine).

DRUGS ACTING ON THE VESSEL WALL, UNRELATED TO NERVE ENDINGS

Nitrites (Organic and Inorganic) and Nitrates (Organic)

Both nitrites and organic nitrates were introduced into medicine in the 19th century: they act on smooth muscle, relaxing it. Their chief use is in angina pectoris. They principally affect:—

The Vascular System. There is a generalised dilatation of arterioles, capillaries and venules resulting in a fall of blood pressure which is postural at first. The drugs are used to dilate the coronary arterioles in angina pectoris. A severe drop in blood pressure will reduce coronary flow as well as cause fainting due to reduced cerebral blood flow, and so it is vital to ensure that an overdose is not taken. Since the blood pressure tends to rise during an anginal attack there is some latitude. Patients should be instructed on the signs of overdose: palpitations, dizziness, blurred vision, headache and flushing followed by pallor, The optimum dose is probably that which causes slight tachycardia and a feeling of fullness in the head.

The Urinary, Biliary and Alimentary Tracts. Transient relief of pain due to spasm of smooth muscle, colic, can sometimes be obtained.

Bronchial Spasm is occasionally relieved by amyl nitrite but this is not a treatment of choice.

Preparations of Nitrites and Nitrates

Glyceryl Trinitrate (trinitrin, nitroglycerin) is an oily, non-inflammable liquid which explodes on concussion with a force greater than that of gunpowder. However, physicians meet it mixed with lactose, sucrose and cocoa and made into a tablet, in which form it is both innocuous and fairly stable. Tablets more than a year old or exposed to heat or air will have lost some or all potency by evaporation. Glyceryl trinitrate is the drug of choice in the treatment of angina pectoris. The tablets should be bitten up and dissolved under the tongue, where absorption is more rapid and reliable than from the intestine. In addition, the drug then reaches the coronary vessels without first passing through the liver, which metabolises it.

The action begins in two minutes and lasts up to 30 minutes. The initial dose is 0·5 mg., but the amount required for each patient must be found by trial, up to 6 mg. a day total. It is taken at the onset of pain or as a prophylactic immediately before any exertion which experience has taught usually brings on the pain. The drug is occasionally given as a diagnostic test for angina pectoris, but it is unwise to use it if myocardial infarction is suspected. Slow-release preparations (*e.g.* Sustac) are available for prophylaxis and these are swallowed; they are less certainly effective.

Amyl Nitrite is an inflammable volatile liquid. It is dispensed in glass capsules (0·2 ml.) which are broken between finger and thumb, the gauze covering preserving the patient from injury and also absorbing the liquid, which is then inhaled through the open mouth for absorption via the lungs. Its action begins almost at once and lasts about three minutes. The capsule is best held in the cupped hands or handkerchief to prevent too rapid vaporisation. Its characteristic smell will draw attention to the user even if he has succeeded in breaking the capsule silently. It frequently causes a deep flush and a throbbing headache. These disadvantages have rendered the drug obsolete in the treatment of angina pectoris, but it is still sometimes worth trying as an antispasmodic in resistant cases of colic and asthma. In cyanide poisoning (p. 432) it is given to induce methæmoglobinæmia.

Octyl Nitrite is similar to amyl nitrite but slightly longer acting. Victims of œsophageal achalasia get relief from inhalations (0·2 to 0·4 ml.) before meals. It relaxes the cardiac sphincter and allows the œsophagus to empty by gravity. It is also inhaled, in the erect position, before going to bed, to avoid overspill pneumonia during sleep. Octyl nitrite is more effective in achalasia than amyl nitrite, as well as being pleasanter to take.

Erythrytyl Tetranitrate is another explosive made safe by mixture with lactose. Taken by mouth (swallowed, or sublingually) the action begins in 15 minutes and lasts up to four hours. It is used as a prophylactic against attacks of angina pectoris but is not a substitute for glyceryl trinitrate in the acute attack. The dose is 15 to 60 mg. 2 to 4-hourly.

Pentaerythrytol Tetranitrate (Mycardol, Peritrate). When erythrytyl tetranitrate was unobtainable in Sweden during the 1939-45 war, this explosive substance was tested and found to produce vasodilatation. Taken by mouth (swallowed or sublingually) the action begins in 10 minutes and lasts five hours. It reduces the frequency and severity of anginal attacks in about one-third of patients. It does not displace glyceryl trinitrate and should be used in conjunction with it. It occasionally causes gastro-intestinal symptoms and should always be taken on an empty stomach. The dose is 10 to 20 mg. three or four times a day.

Triethanolamine Trinitrate is a long-acting nitrate with nothing special to recommend it.

Mannityl Hexanitrate (15 to 60 mg., long acting) and sodium nitrite (30 to 60 mg., shorter acting) are occasionally used but have no special advantages.

Tolerance to Nitrites and Nitrates

This occurs, especially to glyceryl trinitrate, if used regularly and frequently. Change of therapy for up to a week every fourth week will restore sensitivity. Higher doses may be needed towards the end of each period. Tolerance does not occur to pentaerythrytol tetranitrate.

Toxicity of Nitrites and Nitrates

Collapse due to fall in blood pressure resulting from overdose or hypersensitivity may occur. The blood pools in the capillaries and venules and reflex arteriolar constriction may occur in an attempt to restore the blood pressure. Thus it is possible for the patient to be in a hypotensive state due to these drugs yet with constricted arterioles. This may explain why sympathomimetic drugs sometimes do not help a case of nitrite syncope. The patient should be inverted if possible, or if supine his legs should be raised above his head.

These drugs are contra-indicated in myocardial infarction.

Nitrite headache, which may be severe, is probably due to the stretching of pain-sensitive tissues around the meningeal arteries resulting from the increased pulsation which accompanies the cerebral vasodilatation. Tolerance to this effect often develops rapidly, a fact well-known in explosives factories.

Methæmoglobinæmia (p. 405) occurs with heavy dosage.

Other Vasodilators

Xanthine Drugs (caffeine, theophylline) are seldom used as vasodilators, although theophylline, as aminophylline (p. 226) or as choline theophyllinate, is sometimes used in angina pectoris, see below.

Choline Drugs. These produce too many other effects to be clinically useful as vasodilators.

Iproniazid is an inhibitor of the enzyme, mono-amine oxidase, which destroys 5-hydroxytryptamine (serotonin), adrenaline and noradrenaline, in the body. It has therefore been advocated as a coronary vasodilator. There is no good evidence that it is effective in angina pectoris and it has a wide range of toxic effects. This group of drugs causes hypotension, although in theory the opposite would be expected. They are also used in psychiatry, p. 209.

Khellin, from an Egyptian plant, is useless.

There are numerous other peripheral vasodilators which include nicotinic acid (p. 402), papaverine (p. 165), nylidrin (Perdilatal), Hexopal, and these are sometimes useful in peripheral vascular disease, p. 268.

Evaluation of Coronary Vasodilator Drugs (*1*, *3*, *4*)

In a study of electrocardiograms of anginal patients before and after controlled exercise, it has been found that glyceryl trinitrate prevented E.C.G. changes induced by exercise. Pentaerythrytol tetranitrate and erythrytyl tetranitrate were also effective and these two drugs can be commended. Ethyl alcohol, taken as whisky, reduced the pain induced by the exercise test but did not modify the E.C.G. changes, which seems to dismiss the long-held belief that alcohol is an effective coronary vasodilator. It is simply a mild analgesic. Theophylline compounds are often recommended in angina pectoris, but 500 mg. aminophylline i.v. was found to have slight or insignificant effect. It is therefore unlikely that similar compounds recommended for oral use are really effective in angina pectoris (*1*).

Summary of Treatment of Angina Pectoris

1. The cause is treated when possible, *e.g.* syphilis, anæmia.
2. Glyceryl trinitrate is given for acute relief of pain.
3. The patient is encouraged to arrange his life so as to reduce the number of attacks as far as possible.
4. The longer acting organic nitrates may be used as prophylactics.

5. If tolerance develops to glyceryl trinitrate, one of the other short-acting compounds is used for a week.

6. If angina of increasing severity suggests a myocardial infarction anticoagulant therapy is indicated.

7. If attacks of angina occur at rest the induction of myxœdema with ^{131}I or antithyroid drugs may be justified.

Surgical attempts to improve the myocardial blood supply may have a place, but are still experimental.

DRUGS ACTING IN RELATION TO SYMPATHETIC NERVE ENDINGS

Adrenergic Blocking Drugs (5)

Less satisfactory terms for the adrenergic blocking drugs are adrenolytic or sympatholytic.* Adrenergic blocking drugs prevent the response of effector organs to adrenaline and noradrenaline (and other sympathomimetic amines) whether released in the body or injected. They block excitatory actions of adrenaline and noradrenaline, except those on cardiac rate and force of contraction. Inhibitory effects such as bronchodilatation and vasodilatation are unaffected. Circulating adrenaline and noradrenaline are antagonised more readily than the effects of adrenergic nerve stimulation.

The drugs act by competition with adrenaline and noradrenaline for the receptors on the effector organs (they neither alter the substances themselves nor affect their production).

Some of the adrenergic blocking drugs have to be altered in the body before they become effective and this explains the slow onset of action of phenoxybenzamine.

The principal action of adrenergic blocking drugs is to produce peripheral vasodilatation.

Side-effects due to adrenergic block are postural hypotension, nasal stuffiness and red scleræ. Effects peculiar to each drug are mentioned below.

Tolazoline (Priscol)

In addition to its brief and only moderately powerful adrenergic blocking effects, tolazoline has a direct vasodilator action on peripheral vessels. This makes it suitable for use in peripheral vascular disease, although blood flow is increased more in skin than in muscle. It also causes tachycardia by direct action on the heart and stimulates the gastro-intestinal tract, producing diarrhœa. It is a stimulant of gastric acid secretion and may activate dormant peptic ulcers. Nausea and vomiting result from gastric irritation. As with all drugs having such side-effects it should be stopped unless it is certainly doing good.

---

* These terms are sometimes given different and specific meanings.

The dose of the hydrochloride is 25 to 50 mg. orally, i.v. or i.m. four to six times a day.

Phentolamine (Rogitine)

Phentolamine is a short-acting drug chemically related to tolazoline. It has similar effects but less direct vasodilator action. It is principally used in the diagnosis of, and control of hypertension due to, phæochromocytoma (p. 282). It is unreliable when given by mouth and it is usually given i.v. or i.m. (5 to 30 mg. of the methanesulphonate).

Phenoxybenzamine (dibenyline, Dibenzyline)

Phenoxybenzamine is a powerful and specific adrenergic blocking drug whose effects may last two days or longer. Cumulation may therefore occur at the beginning of treatment and the dose must be increased slowly. It is usually impossible to reverse the circulatory effects of an overdose by noradrenaline or other sympathomimetic drugs. The full effect of an i.v. dose may take up to an hour to develop.

It is wise to observe the effects of a single test dose closely before starting regular administration.

Indigestion and nausea are common with oral therapy. The oral dose is 10 to 80 mg. three or four times a day. 10 to 70 mg., according to the response, may be given by i.v. infusion over 20 minutes.

Ergot Alkaloids (see p. 360)

The naturally occurring alkaloids with effective adrenergic blocking actions are also powerful vasoconstrictors and this action obscures the vasodilatation which is characteristic of adrenergic blocking drugs.

Chemical reduction of the natural alkaloids gives derivatives which cause little smooth muscle stimulation and these have been used to produce adrenergic block. They are also thought to reduce sympathetic tone by a depressant action on the central nervous system. The principal preparation is Hydergine (a mixture of three dihydrogenated alkaloids). It is liable to cause malaise, nausea and vomiting at effective doses. Hydergine may increase cerebral blood flow without lowering the blood pressure and its use has been reported to lead to improvement in some cases of cerebral ischæmia.

The dose of Hydergine is 0·5 mg. four to six times a day sublingually. The effects are less reliable if the drug is swallowed. 0·3 to 0·6 mg. may be given s.c.

Chlorpromazine (see p. 205)

This drug has many actions of which adrenergic block is a minor one, but sufficient to cause hypotension as a side effect.

Yohimbine

This is an alkaloid from a West African tree. It is a weak adrenergic blocking agent. It also stimulates the central nervous system, causing a release of antidiuretic hormone. When given with a barbiturate it causes seminal ejaculation in mice, but despite this it is no longer regarded as an effective aphrodisiac in man.

Uses of Adrenergic Blocking Drugs

These include:—

Peripheral Vascular Disease (see below)

Hypertension

a. phæochromocytoma (p. 282).

b. essential: the hypotensive effect tends to wear off. Side-effects are common and these drugs have no place in routine therapy.

Miscellaneous

THE PREVENTION AND TREATMENT OF CARDIAC ARRHYTHMIAS occurring during cyclopropane anæsthesia or following overdose with adrenaline and other sympathomimetic amines.

IN HYPERHIDROSIS; this raises the still unsettled relationship between adrenaline and sweating, for although most sweat glands are supplied by cholinergic (but sympathetic) nerves, adrenaline injected intradermally causes local sweating and patients with phæochromocytoma sweat excessively.

IN CHILBLAINS, with dubious benefit.

IN CAUSALGIA. The mechanism of relief, if and when it occurs, is unknown.

Drugs in Peripheral Vascular Disease

The aim is to produce peripheral arteriolar vasodilatation without a concurrent significant drop in blood pressure, so that an increased blood flow in the limbs will result. Drugs are naturally more useful in patients in whom the decreased flow of blood is due to spasm of the vessels (Raynaud's phenomenon) than where it is due to organic changes in the arterial wall which may render dilatation in response to drugs impossible (arteriosclerosis, Buerger's disease).

Adrenergic blocking agents are widely used in peripheral vascular disease, but they increase skin rather than muscle blood flow ([illegible]). They have been successfully used in the treatment of superficial ulcers (varicose and traumatic).

Drugs do not remove the cause of the disease but may delay the onset of gangrene or limit its spread and relieve some of the symptoms. That treatment is unsatisfactory is shown by the wide range of drugs used. Methacholine, ethyl alcohol, aminophylline, neostigmine, papaverine and ganglion-blocking agents have all been recommended at various times. There are very many other peripheral vasodilator drugs, some of which are named on p. 265. They are worth trying in troublesome cases, but adequate therapeutic trials have not been done and so no definite recommendations can be made. Unsubstantiated claims are rife. Muscular cramps, especially at night, are common in patients with peripheral vascular disease. Quinine sometimes relieves them (p. 78).

DRUGS ACTING ON POSTGANGLIONIC SYMPATHETIC NERVE FIBRES

Bretylium Tosylate (Darenthin). Bretylium (6) is active when taken by mouth; it selectively blocks transmission in post-ganglionic sympathetic (adrenergic) nerve fibres (site 4 in the figure on page 228) and prevents the release of noradrenaline. It does not antagonise the action of injected adrenaline or noradrenaline, and so differs in an important way from the adrenergic blocking drugs. The hypertension of phæochromocytoma may not be reduced by bretylium although it is reduced by adrenergic blocking agents. It seems likely that bretylium is selectively concentrated in the adrenergic nerves.

Bretylium in fact increases the sensitivity of the sympathetic end-organs to adrenaline or noradrenaline, as does sympathectomy, and this may account for the development of tolerance, *i.e.* the adrenaline and noradrenaline released by the suprarenal medulla, or any still produced at the endings of partially blocked nerves, having greater effect than normal.

In therapeutic doses bretylium does not interfere with parasympathetic transmission and so its use in hypertension is not accompanied by the often disabling parasympathetic side-effects of ganglion-blocking drugs. Postural hypotension, of course, occurs.

The oral dose of bretylium tosylate to control hypertension is extremely variable, chiefly because of irregular absorption. The dose needed ranges from 100 mg. three times a day to several grams a day. The initial dose may be 100 mg. three times a day, increased by 100 mg. per dose on alternate days. Many patients are controlled by about 600 to 700 mg. three times a day, and if more than four grams total are needed it may be better to combine bretylium with another drug such as pempidine, reserpine or hydrochlorothiazide to try to reduce the number of tablets to be taken. Side-effects inevitably include postural hypotension which may be especially pronounced with exercise, and also blocked nose, diarrhœa, parotid pain, weakness, nausea, and failure of ejaculation without impotence.

Bretylium alone may fail to control malignant hypertension. Owing to its irregular absorption from the intestine it is prone to cause severe postural hypotension unpredictably and so is not recommended in patients with cerebral or myocardial ischæmia in whom a completely absorbed drug (pempidine, mecamylamine) is probably preferable.

Guanethidine (Ismelin). Guanethidine (*13*) probably acts in the same way as bretylium, but is not related to it chemically. Early experience suggests that a single daily dose may be adequate and that five to seven days should elapse between each increase in dose to avoid undue cumulation.

It is obviously impossible to make any dogmatic statements on the place of drugs such as guanethidine and bretylium in the therapy of hypertension until much more experience has been obtained.

DRUGS ACTING AT AUTONOMIC GANGLIA

Ganglion-blocking Drugs

Drugs which block transmission in autonomic ganglia have been known since 1889, when Langley demonstrated that some of the effects of nicotine were due to ganglion stimulation followed by ganglion block. Many drugs possess some ganglion-blocking activity in addition to their other effects. Only those in which it is the principal or sole action are used clinically to produce ganglion block. The first ganglion-blocking drug to be used at all widely in medicine was tetraethylammonium (TEA) and this was supplanted in 1950 by the methonium group of drugs. The latter are named according to the number of CH_2 groups in a chain, thus, pentamethonium (C_5), hexamethonium (C_6). With the increase in the number of carbon atoms the ganglion-blocking action virtually disappears and is replaced by a neuromuscular-blocking effect as with decamethonium (C_{10}). The methonium ganglion-blocking drugs are highly effective when injected, but absorption from the alimentary tract is unreliable and for oral use mecamylamine and pempidine are preferred.

The ganglion-blocking drugs act by competing with acetylcholine released from the nerve endings in the ganglia, preventing it from exciting the nerve cells. The amount of acetylcholine released is unaffected.

Ganglion-blocking drugs are not destroyed in the body but are excreted unchanged by the kidney. Defective renal function, which is common in hypertension, either as cause or effect, therefore leads to cumulation. Careless administration of these drugs to patients with a raised blood urea may thus have disastrous effects.

Unfortunately there are no drugs which block sympathetic and not parasympathetic ganglia. Thus reduction of sympathetic vasomotor activity by ganglion block can only be achieved at the cost of a wide range of side-effects due to concurrent parasympathetic block. These are frequently disabling and on occasion have even proved fatal. An understanding of the effects of ganglion-blocking drugs requires an elementary knowledge of the physiology of the autonomic nervous system.

Principal Effects of Ganglion-blocking Drugs

These are:—

ON THE CIRCULATION. The blood pressure depends on the peripheral vascular resistance and on the cardiac output. Both of these may be reduced by ganglion blockade so that the blood pressure falls. A reduction of sympathetic arterioconstrictor tone reduces the peripheral resistance. A reduction of sympathetic venoconstrictor tone leads to pooling of the blood in the veins; this reduces the venous return to the heart, especially in the upright position, and cardiac output therefore drops.

These effects are minimal or absent with therapeutic doses in a supine normal subject, who usually shows little more than a slight tachycardia due to vagal block. The supine hypertensive patient usually experiences a moderate drop in blood pressure.

There is little risk of impairing renal function by reducing the blood flow except in patients in whom there is already serious renal insufficiency, when effective control of the hypertension may be accompanied by progressive renal failure.

In sympathectomised patients ganglion block still produces the characteristic vascular changes, probably because of the necessary incompleteness of the operation. Some autonomic fibres synapse elsewhere than in the principal ganglia and so escape the surgeon. Nerve regeneration also occurs.

A patient whose autonomic ganglia are blocked has an abnormal sensitivity to pressor agents such as noradrenaline. This is largely because compensatory autonomic reflexes which would normally control a rise of blood pressure are blocked, but also there may be an actual increase in sensitivity of peripheral arterioles to adrenaline and noradrenaline, an effect which could account for the development of tolerance.

In hypertensive congestive cardiac failure the effects of ganglion block are beneficial, being similar to those of venesection or the application of venous tourniquets to the thighs, all of which cause a reduction of venous pressure.

Ganglion-blocking drugs given i.v. lower the cerebrospinal fluid pressure in cases of hypertensive encephalopathy, with consequent clinical improvement. They must be used for this purpose with caution to avoid excessive reduction of blood pressure. They also reduce pulmonary œdema due to congestive heart failure by reducing venous return to the heart.

On the Alimentary Tract. Salivary secretion is reduced and patients often complain of a dry mouth.

Gastric secretion is reduced and attempts have been made to treat peptic ulcer with these drugs, but the inevitable occurrence of other effects such as postural hypotension makes the treatment impractical. The gastric secretory response to insulin, which is mediated by the vagus, is abolished, but the direct effect of histamine on the secretory cells is not affected.

Motor activity throughout the alimentary tract is reduced. Constipation is common and even paralytic ileus can occur.

On the Eye. It might be expected that the blocking of the parasympathetic constrictor fibres to the sphincter pupillæ would be balanced exactly by the blocking of the sympathetic supply to the dilator, and hence the size of the pupil would not change. However, in fact there is normally a preponderance of parasympathetic tone (as of vagal tone on the heart). Therefore the pupil dilates moderately. Ocular accommodation is also paralysed. A patient may become unable to read or may find that his spectacles no longer suit him.

Skin. Sweating is reduced and the skin is warm due to peripheral vasodilatation. The heat loss through the skin lowers the body temperature; patients taking ganglion-blocking drugs commonly have temperatures below normal.

Genito-Urinary Tract. Bladder paralysis and impotence occur. Victims of prostatic enlargement may develop acute retention of urine.

Individual Ganglion-blocking Drugs

Hexamethonium (as bromide, iodide, chloride or bitartrate) was the first clinically useful drug of this group. It is unsuitable for oral use as absorption is irregular; it is only used on the occasions when an injectable drug is needed, *e.g.* hypertensive encephalopathy, pulmonary œdema. It is important to start with a small dose in these conditions for the patient may be very intolerant indeed. The dose is 2 to 200 mg. s.c. or i.m.; 2 to 50 mg. i.v. The drug is rapidly absorbed when given s.c. or i.m., and maximal effects occur in less than 20 minutes and last from 1 to 3 hours according to the dose.

Mecamylamine (Inversine) is readily absorbed from the alimentary tract. It penetrates inside cells, and produces a range of toxic effects unrelated to ganglion block. It probably does not act by competition with acetylcholine as do the other drugs and its hypotensive effects may be only partly due to ganglion block. Mecamylamine also interferes with the response of muscle, both smooth and voluntary, to acetylcholine, and the constipation that accompanies its use may be promoted by this action. The drug accumulates in the body, bound to intracellular protein, during the first few days of administration and its onset of action is slower than with other ganglion-blocking drugs even when it is given by injection.

In addition to those expected from ganglion block, toxic effects include tremor, weakness, psychosis and diarrhœa.

Excretion is delayed if the urine is alkaline and hastened if it is acid and this can have clinical importance if the urine reaction is being changed deliberately, *e.g.* by potassium citrate, acetazolamide or ammonium chloride.

The oral dose of the hydrochloride is 2·5 to 15 mg. two or three times a day.

Pempidine (Perolysen, Tenormal) (7) resembles mecamylamine in that it is readily absorbed from the alimentary tract. It penetrates into cells and its excretion is delayed in an alkaline urine although acidification of the urine has little effect in hastening excretion. An oral dose provides hypotensive effect after one hour, lasting about six hours. The dose for control of hypertension ranges from 2 to 25 mg. of the bitartrate four times a day. Side-effects, especially constipation, disappear more rapidly after withdrawal of pempidine than after mecamylamine. This is attributed to the fact that less pempidine is bound to protein, from which it is only slowly given up, than is the case with mecamylamine.

Pempidine is probably the least unsatisfactory orally active ganglion-blocking agent for use in hypertension.

Tetraethylammonium (TEA) was rendered obsolete by hexamethonium. It has side-effects unrelated to ganglion block, *e.g.* tingling of hands and feet.

Trimetaphan (Arfonad) is a short-acting agent whose use is almost confined to producing hypotension during anæsthesia. This is sometimes desirable to reduce bleeding in plastic and neurosurgical operations. The drug is given by continuous or intermittent i.v. infusion. The desired blood pressure, usually a systolic of 70 to 80 mm. Hg., is achieved by tilting the patient and adjusting the flow of the solution to give a dose of 1 to 5 mg. of the camphorsulphonate a minute. The blood pressure rises significantly within 10 minutes of stopping the infusion. Intermittent dosage of 10 to 30 mg. every 10 to 50 minutes may be used. If more than 250 mg. is given recovery may be slow.

A solution of trimetaphan is incompatible with thiopentone, gallamine, iodides, bromides and strong alkaline solutions.

In addition to ganglion block, trimetaphan causes vasodilatation both by a direct action and by histamine release.

Induced hypotension is dangerous, especially if prolonged, and deaths have occurred from renal failure and coronary and cerebral thrombosis in the arteriosclerotic and the very young.

Other available ganglion-blocking drugs are pentolinium (Ansolysen), chlorisondamine (Ecolid), and trimethidinium (Baratol).

Potentiation of Ganglion-blocking Drugs

Reserpine and chlorothiazide potentiate the hypotensive but not the other effects of ganglion block. They are used in hypertension to reduce the incidence of unwanted actions, by enabling the dose of ganglion-blocking drug to be reduced. Renal failure and hypothermia potentiate ganglion-blocking drugs; so does alcohol, by inducing peripheral vasodilatation. Sodium depletion also potentiates the hypotensive effect of ganglion-blocking agents and this may be important when diuretics are used in hypertensive patients.

Tolerance to Ganglion-blocking Drugs

This occurs, usually over a period of weeks. If it is unnoticed or neglected it can be the cause of failure of treatment in hypertension. If, for any reason, a patient ceases to take one of these drugs for a few days, tolerance will be lost and treatment should be restarted at a low dose.

Toxicity of Ganglion-blocking Drugs

The ganglion-blocking drugs are remarkably non-toxic apart from their autonomic effects, but unwanted actions (side-effects) occur in most patients due to the virtual absence of selectivity for the different ganglia. The commonest of these effects are mentioned above.

Ocular accommodation may be partly restored by eye-drops containing choline drugs, *e.g.* pilocarpine, but the prescription of special glasses after stabilisation of the dose for several months is often more satisfactory.

For constipation an oral dose of neostigmine as required is sometimes satisfactory. Liquid Paraffin and Magnesium Hydroxide Emulsion, B.P.C., may also be used, or something stronger such as a reliable preparation of senna. It is absolutely essential to control constipation due to ganglion-blocking drugs for it can develop into a paralytic ileus which persists even if the drug is stopped, and this can be fatal.

The following case shows the difficulty of recognising the toxic effect of a new drug for what it is when little is known about it. A middle-aged hypertensive man treated with pentamethonium (an analogue of hexamethonium) presented with symptoms of intestinal obstruction. "It was realised that this drug could cause vomiting, distension and constipation but no previous reports had described abdominal pain or X-ray findings characteristic of obstruction; consequently it was felt unwise to withhold laparotomy . . . . Laparotomy revealed that the whole of the small gut was grossly distended . . . cæcum and large gut were of normal calibre." The gut was emptied of gas by puncture. "It was remarkable that, after deflation, the gut did not contract . . . it merely became more flaccid . . . there was no improvement . . . He died 48 hours after operation."* If ileus does occur it would probably be wise to start intestinal suction and to give frequent, say hourly, injections of neostigmine s.c.

The patient should be warned of the dangers of straining to open his bowels, for this is to perform Valsalva's manœuvre, and the resultant rise in intra-thoracic and intra-abdominal pressure compresses the great veins, the return of blood to the heart falls or even ceases, cardiac output drops and the patient faints. Recovery from the faint is delayed and this may be serious in arteriosclerotic subjects. The onset of fainting and the delayed recovery are enhanced by the absence of the normal compensatory vascular reflexes.

Excessive hypotension or circulatory collapse may occur with ganglion-blocking drugs. It should be treated in an emergency by inverting the patient. If this does not restore the blood pressure, phenylephrine or a similar drug (p. 256) should be given intermittently i.v. or i.m., according to the response.

Uses of Ganglion-blocking Drugs

These may be summarised:—

In Hypertension, see p. 279–282.

In Acute Pulmonary Œdema due to hypertensive cardiac failure.

To Produce Hypotension for Bloodless Surgery, see under trimetaphan, p. 273.

In Peripheral Vascular Disease. Adrenergic blocking drugs are to be preferred, p. 268.

Miscellaneous. Minor uses of dubious value include pink disease, causalgia, colic and hiccoughs.

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

Rauwolfia

Plants of the Rauwolfia genus grow in India and South-East Asia where they have been considered, since ancient times, to have medicinal properties, being used for snake-bite, insomnia and insanity.

In 1933 hypotensive activity was demonstrated in an alkaloid from

---

* Goldstone, B. (1952). *S. Afr. med. J.*, **26**, 552.

Rauwolfia serpentina in India, where preparations of the plant were in wide use.

Interest in rauwolfia preparations was only aroused in Western countries about 1950. Extensive chemical, pharmacological and clinical studies have since been made. The pure alkaloid reserpine is available and there are no special indications for using the cruder preparations of the root of Rauwolfia serpentina. Numerous preparations containing mixtures of rauwolfia with other hypotensive drugs are available but on the whole they are undesirable, as are nearly all such preparations, because the dose of the constituents cannot be varied independently.

Reserpine (Serpasil). This alkaloid is chemically related to yohimbine, which also occurs in R. serpentina, but differs from yohimbine in having no peripheral adrenergic blocking effects.

Reserpine acts on the central nervous system. Electrical stimulation of the anterior hypothalamus near the parasympathetic centre produces sleep, miosis, bradycardia and decreased peripheral vascular resistance. Since reserpine produces all these effects, it seems likely that it may exert its principal action in this neighbourhood. It is thought to depress the sympathetic centre.

Reserpine also has a peripheral action on arterioles, large doses depleting them of noradrenaline stored in their walls. If this occurs at clinical dose levels it might contribute to the hypotensive effect. In addition reserpine causes release of 5-hydroxytryptamine in the brain and other parts of the body where this substance is found. These effects are of great interest but cannot at present be used to explain all the effects of the drug.

There is a delay in the onset of action of reserpine of at least one to two hours after an i.v. injection and, depending on the dose, of several days after commencing oral administration. This suggests an indirect mechanism of action. Cumulation occurs and the effects wear off over several days.

The Effects of Reserpine

These are principally on:—

The Central Nervous System. Sedation is produced, which differs from that induced by barbiturates. Subjects do not go to sleep unless their surroundings are conducive, and they are easily rousable. Irritability and aggressiveness are reduced in both man and animals (Siamese fighting fish stop fighting). Anxiety is lessened and the drug is sometimes used as a tranquilliser. Subjects continue to be able to think clearly. Mental depression often occurs with more than minimal doses and suicide has been reported with heavy doses. States of anxiety and excitement rarely occur.

Reserpine potentiates barbiturates.

The Cardiovascular System. A moderate degree of hypotension occurs, which is greater in hypertensive than in normotensive subjects (as with ganglion-blocking drugs). Bradycardia, which is antagonised by atropine, and reduction of peripheral vascular resistance occur. The cardiac output and renal blood flow are not significantly altered.

Homœostatic reflexes are not blocked by reserpine as they are by ganglion-blocking drugs. Reserpine however potentiates the hypotensive effect of ganglion block and this effect is used in the treatment of hypertension.

Other Effects include: increased intestinal peristalsis and increased gastric secretion of acid.

Toxicity of Reserpine

Reserpine is comparatively safe apart from its mental depressant effects, which are more dangerous in patients liable to endogenous depression. The lethal dose is unknown but a boy aged 20 months has survived 260 mg. with little more than marked sleepiness for 36 hours. Experimental animals die of respiratory depression.

Toxic effects are fairly common: lethargy and apathy, nasal stuffiness, gain in weight and diarrhœa. Dyspnœa not associated with cardiac failure occurs, and onset of cardiac failure has also been reported. Fluid retention with œdema occurs occasionally in the absence of cardiac failure.

With large doses an extrapyramidal syndrome clinically indistinguishable from Parkinsonism occurs. However, it is reversible and is controlled by anti-parkinsonian drugs, although it is preferable to stop the drug. Decreased libido and nightmares may occur. Epileptics may have more fits.

Peptic ulcers may be activated.

The Uses of Reserpine

Reserpine is a pure alkaloid which is well absorbed from the alimentary tract; parenteral preparations are available but seldom required. It is used as a tranquilliser and as a hypotensive agent. Alone it can control only mild cases of hypertension. In severe cases it is used to provide synergism with, or potentiation of, other hypotensive drugs. Small doses (0·3 to 0·5 mg. a day) should be used in hypertension because of the risk of mental depression. In psychiatry larger doses (0·75 mg. a day) are used in agitated patients. In acutely excited patients in hospital, 10 mg. i.m., plus 3 mg. orally, have been used.

Rescinnamine and Deserpidine (Harmonyl) have not been shown to offer significantly different therapeutic effects from reserpine.

Hydralazine (Apresoline)

The exact site of action of hydralazine in the central nervous system is unknown. Indeed some dispute that it acts there at all.

Hypotension which is predominantly postural and seldom severe, is accompanied by tachycardia, decreased peripheral vascular resistance and often by a brief increase of renal blood flow. The latter is inconstant and does not amount, despite claims, to a practical advantage.

Side-effects are common: headache, nasal and conjunctival congestion, lachrimation, flushing, palpitations and vomiting. Hypersensitivity reactions occur.

Anginal attacks are sometimes precipitated. With heavy (over 600 mg. per day) and prolonged (over 6 months) dosage a rheumatoid arthritis-like syndrome may occur and if the drug is unwisely continued a clinical and pathological picture resembling acute disseminated lupus erythematosus follows. Recovery occurs, but sometimes only with the help of adrenocortical steroids. Since this disorder is related to dosage and to duration of administration, and since it may or may not recur on subsequent re-administration of hydralazine it is probably not due to hypersensitivity.

Tolerance may occur, especially to the side-effects.

Hydralazine is used only in hypertension. It is not very effective and is usually given in combination with another hypotensive drug.

The dose of hydralazine hydrochloride is increased gradually, *e.g.*:—

10 mg. orally four times a day, after meals (to reduce incidence of nausea and vomiting) for four days,

then 25 mg. four times a day for the next seven days,

then 50 mg. four times a day for the next seven days and so on to a maximum of 400 mg. total in a day.

DRUG ACTING AT AFFERENT NERVE ENDINGS

Veratrum

Veratrum preparations are of greater theoretical interest than practical importance. Preparations of the plants Veratrum viride and album (green and white hellebore) which are used in the treatment of hypertension contain a number of alkaloids (including veratridine and protoveratrines A and B).

These alkaloids stimulate nerve receptors in the coronary vessels and ventricular wall. Impulses pass up vagal afferent fibres to the medulla. Such stimulation leads to a vagal bradycardia (abolished by atropine), also to hypotension which is accompanied by decreased peripheral vascular resistance (not abolished by atropine). This is called the Bezold-Jarisch effect. The nervous pathway mediating the hypotension is unknown; there is probably an inhibition of sympathetic vasoconstrictor tone. Normal vasomotor reflexes such as the cold pressor effect, are not altered and postural hypotension is unusual.

Other effects of veratrum include:—

a. Cardiac arrhythmias which are abolished by atropine and so are principally vagal, although there is also a direct effect on the heart. Digitalis makes these arrhythmias worse.
b. Bradypnœa due to stimulation of pulmonary stretch-receptors.
c. The production of repetitive discharge in experimental preparations of peripheral nerve and muscle, an effect which has long fascinated physiologists but which is of no clinical importance.
d. Vomiting, probably another reflex effect from vagal afferent endings, and the commonest clinical toxic effect.

The use of veratrum preparations in hypertension is limited by the fact that the therapeutic dose is very close to the toxic dose. Excessive hypotension is rare. In addition to nausea and vomiting, salivation, "heartburn", mental confusion and blurred vision may occur. Concurrent administration of phenobarbitone may reduce toxic effects.

There are a number of veratrum preparations of which Veriloid, a semi-purified mixture of alkaloids (3 to 5 mg., orally three times a day) and protoveratrines A and B (0·5 to 1·5 mg., four times a day) are representative. Parenteral preparations exist.

TREATMENT OF HYPERTENSION

The only curable forms of hypertension are those amenable to surgery, that is those due to unilateral renal disease, phæochromocytoma, Cushing's syndrome, coarctation of the aorta and Conn's syndrome. These should be considered and excluded in every case of severe hypertension.

The prognosis in untreated malignant hypertension is so bad that it was unjustifiable not to treat all such patients when ganglion-blocking drugs became available. Thus in the clinical trials of the use of hexamethonium in hypertension the controls had to be similar patients observed in previous years. In a series of 82 patients suffering from malignant hypertension treated with ganglion-blocking drugs the expectation of life was six to eight times that of patients not so treated (*8*).

The aim of treatment is to reduce the blood pressure to as near normal levels as possible in the erect posture, and to keep it there. When this is achieved there is usually very great symptomatic improvement, retinopathy clears and vision improves; headaches are often abolished. However, a variable amount of irreversible damage has often been done by the high blood pressure before treatment is started, renal failure may progress despite treatment, arterial damage leads to cardiac or cerebral catastrophies. It is obviously desirable to start treatment before irreversible changes occur even if symptoms do not demand relief.

Thus any patient with malignant hypertension, or very severe hypertension likely to become malignant, or with disabling symptoms, certainly requires effective drug treatment. Such treatment requires at least as much care and attention as the use of insulin in diabetes.

Whether patients with mild essential hypertension should be treated with drugs is a problem which vexes physicians. Unfortunately the prognosis of the disease untreated cannot be predicted for the individual and so the decision to submit a patient to the inconveniences of continuous drug therapy is not one to be taken lightly. As more reliable and non-toxic drugs are discovered it is likely that more patients with less severe hypertension will receive drug treatment, but whether this is desirable it is impossible to say, as no adequate controlled investigations have been done.

In one substantial unselected series of patients of all grades of severity followed over 13 years, the mortality rate of those treated by drugs or sympathectomy did not exceed one-third that of the untreated group (*9*).

On the other hand in another series of patients with initial diastolic pressure above 120 mm. Hg., it was found that while reduction of blood pressure in those with hypertensive retinopathy was associated with substantial reduction in morbidity and mortality, in patients with cerebral or cardiac vascular lesions no obvious benefit followed the use of drugs (*10*).

Drugs have almost supplanted sympathectomy in the treatment of hypertension, although the operation may still have a place in young men. If it fails, medical treatment is still effective. In a few patients with severe hypertension lowering the blood pressure may make the patient worse, for instance if there is severe renal impairment (blood urea over 100 mg./100 ml.), advanced cerebral or coronary arteriosclerosis. In these cases blood flow to vital organs may depend solely upon a high perfusion pressure, but when such patients have severe hypertensive symptoms a very cautious trial of hypotensive drugs is worth while. Weight reduction in an obese hypertensive patient often relieves breathlessness on exertion and sometimes lowers the blood pressure, although this may be more apparent than real since arm thickness affects sphygmomanometer readings.

Choice of Drugs in the Treatment of Hypertension

When it has been decided that drug therapy is necessary an attempt should first be made to control the blood pressure with one drug alone as this is both more desirable and more convenient than polypharmacy. In mild cases where symptoms yet demand hypotensive therapy barbiturate sedation or reserpine may suffice. Moderately severe cases may be started on bretylium* or pempidine and, if control is inadequate at high doses, or if side-effects are disabling at the minimal dose required to give control, then a second drug may be added. Perhaps chlorothiazide is the best to use, or one of its analogues if small tablets are particularly desired. (It will be necessary to add potassium chloride to avoid potassium deficiency.) Many patients can be well-controlled on a combination of chlorothiazide and pempidine or chlorothiazide and bretylium. Pempidine with bretylium has been reported to be an effective combination. Chlorothiazide alone is effective in some patients.

Alternatively reserpine with chlorothiazide, pempidine or bretylium will serve for many patients. The choice of a pair from amongst the above drugs is less important than the skill and care with which they are used. Good control of the blood pressure involves seeing the patient often and measuring his blood pressure supine and after standing for a minute to determine the amount of postural fall. It is often neither possible nor desirable (see above) to reduce the blood pressure to normal levels, especially in the elderly and those who have had serious vascular complications. A moderate drop may be enough both to relieve symptoms and prolong life.

In malignant hypertension a ganglion-blocking drug is probably still essential in most cases.

In hypertensive encephalopathy treatment is urgent and hexamethonium by injection may be used for the first few days to provide more rapid and certain control than is obtainable by oral hypotensive agents. Amylobarbitone i.m. or i.v. is useful for the fits.

Every conceivable drug and combination of drugs has been tried and advocated in hypertension.

Hydralazine, phenoxybenzamine and veratrum may be useful sometimes, when other drugs fail. Sodium deprivation (rice diet) is seldom useful as it has to be so strict as to be very unpleasant.

Much published work is invalid because the methods of assessment used were not such as to allow definite conclusions to be drawn on the effect of the drugs. This is largely because of the very great natural variations in the disease. Emotion may result in changes of up to 100 mm. Hg. systolic and 40 mm. diastolic over a period of minutes. In addition these changes may persist for weeks. In therapeutic trials the short period of control observation of about a month which often precedes six months' treatment is valueless for comparative purposes. "A period of treatment is a period of reassurance to a hypertensive patient, and reassurance will obviously lead to greater emotional calmness and a

* Guanethidine may be substituted for bretylium.

lowering of blood pressure. . . . I have seen many patients whose blood pressure at the first visit may be, for example, 260 systolic and 120 diastolic, and at a second visit, a few weeks later, may be 118 systolic and 80 diastolic after only mild sedation and great reassurance. I have given placebos to hypertensive patients and obtained 80 per cent symptomatic improvement." Ayman, who wrote the above words (*11*), has also shown that merely increasing the frequency of a patient's visits to the physician can result in a drop in blood pressure, presumably due to the reassuring effect of such frequent contact. "Yet this scheme of increased frequency of visits is commonly applied by clinical investigators of new drugs. . . ." He also points out that in evaluating sympathectomy "the glaring defect is the usual brief control period of observation before operation".

It is clear that double-blind carefully controlled studies are essential when evaluating the response to treatment in hypertension, especially over short periods, for effective hypotensive drugs are capable of causing serious harm and it is important that only those who will actually benefit from their pharmacological effects should take them.

Phæochromocytoma

This is a rare tumour of adrenal medullary tissue. The principal symptoms and physical signs can be deduced from the fact that it secretes a mixture of adrenaline and noradrenaline.

Tests for phæochromocytoma include:—

The Phentolamine Test. 5 mg. of the methanesulphonate is given into the tubing of an i.v. infusion. If, as in phæochromocytoma, the high blood pressure is due to circulating adrenaline or noradrenaline, then phentolamine lowers it within two minutes by at least 35 mm. systolic and 25 mm. diastolic, or to normal levels, the effect persisting for at least five minutes.*

The Histamine Test. The equivalent of 0·05 mg. base is given into the tubing of an i.v. infusion. This stimulates the tumour to secrete, and hence causes a brisk rise of blood pressure, often preceded by a brief fall. It sometimes precipitates a typical paroxysmal attack. Phentolamine should be available to terminate this if necessary. In a normal there is a brief drop followed by an overshoot of not more than about 10 mm. Hg. systolic. The histamine test should not be used in the presence of severe hypertension.

Estimation of Adrenaline and Noradrenaline, or their metabolites, in the urine is the best single test for phæochromocytoma.

At Operation anæsthesia and manipulation of the tumour leads to liberation of huge amounts of adrenaline and noradrenaline. Phentolamine is essential to control the consequent rise in blood pressure. Once the veins draining the tumour have been clamped noradrenaline may be essential to maintain the blood pressure. An alternative is to prepare the patient for several days before surgery with phenoxybenzamine so that he goes to operation in a complete state of adrenergic blockade. If this is done he must be kept supine throughout.

---

* The test is useless in the absence of sustained hypertension.

Guide to Further Reading on Hypotensive and Vasodilator Drugs

(*1*) Russek, H. I., Zohman, B. L., and Dorset, V. J. (1955). Objective evaluation of coronary vasodilator drugs. *Amer. J. med. Sci.*, **229**, 46.

(*2*) Editorial (1955). Treatment of angina pectoris. *Lancet*, (*i*), 852.

(*3*) Riseman, J. E. F., *et al.* (1958). Nitroglycerin and other nitrites in treatment of angina pectoris: comparison of six preparations and four routes of administration. *Circulation*, **17**, 22.

(*4*) Dewar, H. A.. Horler, A. R., and Newell, D. J. (1959). A clinical trial of pentaerythritol tetranitrate, a Khellin derivative and iproniazid in angina of effort. *Brit. Heart J.*, **21**, 315.

(*5*) Nickerson, M. (1949). The pharmacology of adrenergic blockade. *Pharmacol. Rev.*, **1**, 27.

(*6*) Dollery, C. T. *et al.* (1960). Bretylium tosylate in the treatment of hypertension. *Lancet*, (*i*), 296.

(*7*) Harington, M., Kincaid-Smith, P., and Milne, M. D. (1958). Pharmacology and clinical use of pempidine in the treatment of hypertension. *Lancet*, (*ii*), 6.

(*8*) Harington, M., Kincaid-Smith, P., and McMichael, J. (1959). Results of treatment in malignant hypertension. *Brit. med. J.*, (*ii*), 969.

(*9*) Leishman, A. W. D. (1959). Hypertension—treated and untreated. *Brit. med. J.*, (*i*), 1361.

(*10*) Newman, M. J. D., and Robertson, J. I. S. (1959). Some aspects of prognosis in treated hypertension. *Brit. med. J.*, (*i*), 1368.

(*11*) Ayman, D. (1949). Critique of reports of surgical and dietary therapy in hypertension. *J. Amer. med. Ass.*, **141**, 974.

(*12*) Gillespie, J. A. (1959). The case against vasodilator drugs in occlusive vascular disease of the legs. *Lancet*, (*ii*), 995.

(13) Leishman, A. W. D. *et al.* (1959). Guanethidine, hypotensive drug with prolonged action. *Lancet*, (*ii*), 1044.

Chapter 16

DIGITALIS, QUINIDINE, PROCAINAMIDE

DIGITALIS AND OTHER CARDIAC GLYCOSIDES

"We think the Public under great obligations to Dr. Withering . . . ."
(From a 1785 review of An Account of the Foxglove, by William Withering.)

In 1775 Dr. William Withering was making a routine journey from Birmingham, his home, to see patients at the Stafford Infirmary. Whilst the carriage horses were being changed half way he was asked to see an old dropsical woman. He thought she would die and so some weeks later when he heard of her recovery he was interested enough to enquire into the cause. Recovery was attributed to a herb tea containing some twenty ingredients amongst which Withering, already the author of a botanical textbook, found it "not very difficult . . . to perceive that the active herb could be no other than the foxglove." He began to investigate its properties, trying it on the poor of Birmingham, whom he used to see without fee each day. The results were inconclusive and his interest flagged a little until one day he heard that the principal of an Oxford College had been cured by foxglove after "some of the first physicians of the age had declared that they could do no more for him." Pursuing his investigation, Withering found that foxglove extracts caused diuresis in certain oedematous patients. He defined the type of patient who might benefit from it, and, equally important, he standardised the preparation of his foxglove leaf preparations and was able to lay down accurate dosage schedules. His advice, with little amplification, would serve today. Crude foxglove preparations are called "digitalis."

Considerable skill and practice are needed to get the best results from digitalis and Withering knew this when, after ten years study, he wrote "it is better the world should derive some instruction, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable."* In other words, digitalis, like most potent therapeutic agents can be a potent poison if misused. What Withering feared might happen, did happen; physicians ignored his instructions based on careful observation and long experience, poisoned their patients and complained that Withering was mistaken.

---

* Withering, W. (1785). An Account of the Foxglove. London: Robinson.

After seeing how other physicians used digitalis Withering observed "shall we wonder then that patients refuse to repeat such a medicine, and that practitioners tremble to prescribe it."

The result was that digitalis fell into disrepute although it continued to be used in various diseases, including tuberculosis. 150 years were to pass before it finally became accepted as the valuable asset that it is, and the details of its use in heart failure were worked out again and extended to cardiac arrhythmias.

Digitalis owes its effects to a number of glycosides (digitoxin, digoxin, lanatosides) whose effects are qualitatively similar, differing principally in rapidity of onset and duration of effects. In the present description of its actions, the term digitalis is used to cover all cardiac glycosides. In prescribing it is necessary, of course, to specify the exact preparation intended.

The ways in which digitalis induces the changes in cardiac function described below are not certainly known. Digitalisation leads to a loss of potassium from myocardial cells and some cardiac effects of severe digitalis poisoning may be reversed by administration of potassium. Conversely a low serum potassium, which may be induced by vigorous diuretic therapy, is liable to potentiate digitalis. Calcium increases digitalis effects in animal experiments, so if calcium must be given by i.v. injection to digitalised patients caution is obviously desirable.

Effects of Digitalis

The effects of digitalis may be summarised:—

1. Direct stimulation of failing myocardium leading to increased cardiac output.
2. Reduction in size of dilated heart leading to increased efficiency, *i.e.* more work per ml. oxygen consumed.
3. Increased myocardial excitability leading to ectopic beats, ventricular tachycardia.
4. Depression of conducting tissue with increased refractory period which protects the ventricles from excessive bombardment in auricular arrhythmias, but may cause bradycardia and sometimes even heart-block.
5. Increased vagal activity leading to:—
    a. Decrease in auricular refractory period with conversion of flutter to fibrillation.
    b. Delay in auriculo-ventricular conduction (effects as above).
    c. Bradycardia.

Therapeutic doses of digitalis have no effect on the normal heart.*

---

* SELZER, A., *et al.* (1959). *Brit. Heart J.*, **21**, 335.

High doses in normals cause ectopic beats, arrhythmias and heart-block.

1. **Direct Stimulation of a Failing Myocardium** with increased force of contraction occurs. There is a greater stroke output in a shorter systole which allows a longer diastolic rest for a given cardiac output. Digitalis increases the work done by the dilated and failing heart without increasing its oxygen consumption. This is the principal therapeutic action of digitalis in heart failure and is quite different from that which is made use of in controlling auricular fibrillation.

2. **Reduction in Size of a Dilated Failing Heart** occurs simultaneously with the increase in work. It is probably due to active shortening of myocardial fibres (increased diastolic "tone") and also to reduction of the distending force (venous pressure). Venous pressure is probably lowered by a combination of the effects of increased cardiac output and of the decreased plasma volume resulting from the diuresis consequent on improvement of renal circulation.

The reduced diastolic size is important because it results in an increased efficiency, it being established that a contracting sphere, if small, needs less energy to expel a given volume of fluid than it does if large (8, 9), and that this is probably relevant to cardiac function.

3. **Increased Myocardial Excitability** carries no therapeutic benefit. With high doses ventricular ectopic beats occur and give rise to the classic digitalis-induced arrhythmia, coupled beats or bigeminal pulse, when each normal beat is followed closely by an ectopic ventricular beat which is followed by a compensatory pause. Beats thus occur in pairs. Regular coupling may not occur and the appearance of any ectopic beats in a patient on digitalis gives food for thought. If the ventricular ectopic beats show complexes of different shape on the electrocardiogram, that is, if there is more than one focus in the ventricle initiating impulses (multifocal ectopic beats), there is risk of ventricular tachycardia and fibrillation and action must be taken (see under toxicity). Sympathomimetic amines and aminophylline also increase cardiac excitability, and so are liable to cause arrhythmias in digitalised patients. They should therefore be used cautiously.

Digitalis increases the refractory period of the denervated auricle, but this is of no therapeutic importance as the vagal effect of digitalis acts in the opposite direction to shorten the auricular refractory period and is dominant. In the ventricle digitalis shortens the refractory period and this may contribute to the occurrence of ventricular fibrillation which is the usual cause of death in digitalis poisoning.

4. **Depression of Conducting Tissue.** The refractory periods of the auriculo-ventricular node and bundle of His are increased and conduction time is slowed by direct action of digitalis (prolonged P-R interval on the

electrocardiogram). In therapeutic doses this has no effect on the normal heart rate. In auricular fibrillation the result is to protect the ventricle from bombardment with the too numerous impulses which cause it to contract before diastolic filling is complete. With toxic doses heart-block may occur. The vagal stimulant action of digitalis also slows conduction.

Heart rate in auricular flutter is controlled by the same action as in fibrillation, but in addition the flutter may be abolished by the vagal effect on the refractory period of auricular muscle, see below.

5. **Increased Vagus Nerve Activity.** The site of this action is not agreed. It may be on the vagus centre, on afferent nerve endings or on the efferent endings in the heart itself. The vagal action of digitalis is prominent in auricular fibrillation, but in heart failure the cardiac slowing is probably mostly due to the improved circulation lessening the anoxia of the myocardium which may have caused a reflex tachycardia. Vagal activity slows passage of impulses in the auriculo-ventricular conducting system. Vagal slowing can be differentiated from that due to direct action on conducting tissue or to relief of myocardial anoxia by blocking the vagal nerve endings with atropine. At lower doses vagal predominates over direct effect. At higher doses the heart remains slow in the presence of atropine. Digitalis does not depress the sino-auricular node except in toxic doses.

In addition vagal stimulation shortens the refractory period of auricular muscle and increases the speed of auricular impulse conduction. This overcomes the direct action of digitalis on auricular muscle which is to lengthen refractory period. Whether this effect is responsible for converting auricular flutter into fibrillation as commonly occurs with digitalis is uncertain.

When treating auricular arrhythmias the number of impulses reaching the auriculo-ventricular node may thus be actually increased, but the effects, both vagal and direct, on the conducting system predominate so that the required degree of conduction block can be achieved.

The Electrocardiographic Effects of digitalis are as follows:—The T wave becomes smaller, disappears or may become inverted. The S T segment sags below the iso-electric line. The P–R interval is prolonged (delayed conduction). The Q–T interval is shortened (shorter ventricular systole).

Other Effects of Digitalis. In ordinary doses the blood pressure is not affected and any change is secondary to improvement of heart failure. There is no direct effect on the kidney, diuresis being secondary to improvement in the renal circulation. Thus a rise of blood pressure may occur if it is low due to heart failure, or, if the pressure is abnormally high, as it is in some cases with intense peripheral vasoconstriction, it will be lowered towards normal. However, a large i.v. dose of strophanthin or digoxin may occasionally cause a transient rise of blood pressure by stimulating the myocardium.

Absorption and Metabolism of Digitalis

Digitalis is well absorbed from the alimentary tract when taken orally or by the rectum, which route may be useful in cases of persistent vomiting when this is not due to digitalis toxicity. Pure glycosides may be given i.v. or i.m.

The Fate of Digitalis has been studied using a radio-active glycoside (digitoxin) obtained by growing digitalis purpurea in an atmosphere containing radio-active carbon dioxide. It seems that it is not selectively concentrated in the heart muscle as was previously thought, therefore its action on heart muscle is due to a peculiarity of the muscle, not to there being merely a higher concentration of a drug which would effect all muscle. The glycosides are partly broken down, but mostly slowly excreted unchanged in the urine, and on the rate at which this occurs depends their duration of action. This varies for different glycosides and is important, since the frequency of dosage depends on it. Digitoxin is notoriously cumulative, the action of a single dose persisting two or three weeks (see table, p. 290) so that daily administration is liable to build up toxic levels if not carefully regulated. It is therefore important to ask patients if they have had digitalis recently prior to giving a full digitalising dose.

Uses of Digitalis

These may be summarised:—

1. **In Congestive Cardiac Failure,** acting chiefly by the direct stimulant action on the myocardium.

2. **In Auricular Fibrillation,** acting chiefly by vagal and direct effects on conducting tissue.

3. **In Paroxysmal Tachycardia,** acting chiefly by vagal effects on the sino-auricular node and on the conducting tissue.

4. **In Auricular Flutter,** acting chiefly by vagus nerve effect on the refractory period of the auricular muscle (shortened), to convert flutter to fibrillation.

Preparations of Digitalis

The principal preparations are included in the table, p. 290. The pure substances digoxin and digitoxin are now the most widely used, but excellent results can, of course, be obtained with a crude preparation of the dried leaf.

Digoxin is available as a tablet, an injection solution and as a suppository.

Prepared Digitalis (digitalis folia, a dried leaf preparation) is available as a tablet. Digitalis tincture is obsolete because it sometimes loses activity in storage and because the small volumes taken are difficult for patients to measure accurately.

Digitoxin is available as a tablet, an injection solution and as a suppository.

Lanatoside C (Cedilanid) is available as a tablet, it is unstable in solution and the deacetyl derivative, deslanoside, is given by injection and by suppository.

Ouabain (strophanthin-G) is obtained from a strophanthus plant and is available as an injection solution. It is unreliable when given orally. Strophanthin-K is a mixture of glycosides of variable potency. The word strophanthin used alone is therefore liable to misinterpretation and should be avoided.

Acetylstrophanthin is reliably absorbed after oral administration. After injection its action appears in a few minutes and lasts up to two hours. It is used experimentally only.

The Choice of a Preparation of digitalis is usually easy. Digoxin or digitoxin are satisfactory for all purposes and there is usually no need to consider any other preparation. Prepared Digitalis has no advantage beyond being very slightly cheaper than digoxin. The other preparations only need to be considered in special cases, for instance, in those rare patients who vomit on low doses of the above preparations it may be possible to obtain effective digitalisation with lanatoside C by mouth without inducing vomiting.

There are yet other digitalis preparations, often mixtures of glycosides, which have confusing names and which, since they offer no advantages over the preparations named above are best avoided. Digitalin or digitaline especially should be shunned as it may be any one of a number of preparations of varying composition and dose. Nativelle's Crystallised Digitaline is pure digitoxin. Various other substances with digitalis-like action occur in nature. Little success has attended attempts to use them in therapeutics. They have found their sole application as weapon and ordeal poisons (7).

Biological Standardisation of crude digitalis preparations against an international standard is necessary as chemical methods can only be used on pure glycosides. The death rate in groups of frogs used to be the "official" method until it was demonstrated that it bore little relation to therapeutic potency and that preparations could be "legally weak but therapeutically strong" (3). Cats were substituted, with slight improvement. Digitalis can be assayed in man using either the effect on the heart rate in auricular fibrillation or electrocardiographic changes. The duration of action of the different glycosides has also been measured using these parameters.

Administration and Dosage

Digitalis is given by mouth whenever possible, and by slow i.v. injection of a diluted solution if there is haste. A solution suitable for i.m. use is available (Lanoxin). Suppositories exist. The optimum dose of digitalis

THE DOSAGE AND DURATION OF ACTION OF THE PRINCIPAL CARDIAC GLYCOSIDES

Glycoside (Source)	*After single i.v. digitalising dose:*		*i.v. digitalising dose*	*Total oral digitalising dose given in 3–4 doses 6 hrs. apart*	*Total daily oral maintenance dose*	*Remarks*
	Time of max. effect	*Duration of effect*				
digoxin (from digitalis lanata)	3 hrs.	5 days	0·75–1·0 mg. (or i.m.)	2·0–4·0 mg.	0·25–1·0 mg.	Satisfactory for all routine therapy
digitoxin (from digitalis purpurea)	8 hrs.	18 days	1·0–1·2 mg.	1·0–1·5 mg.	0·05–0·2 mg.	Satisfactory for all routine therapy; very cumulative
lanatoside C (from digitalis lanata)	3 hrs.	5 days	1·2–1·6 mg. (or i.m.)	5·0–10·0 mg.	0·5–2·0 mg.	Said to cause less vomiting and so used in cases of intolerance to other glycosides
ouabain or strophanthin-G. (from 2 African shrubs)	1 hr.	1½ days	0·25–1·0 mg.	erratically absorbed so not used orally	—	Most rapid onset of action, useful in emergency
prepared digitalis (a crude preparation of d. purpurea leaf)	6 hrs. (after or	16 days al dose)	cannot be given by injection	2·0 G.	60–100 mg.	Satisfactory for routine oral therapy. Very cumulative because it contains digitoxin

A full digitalising dose should not be given if digitoxin or prepared digitalis have been taken in the previous 14 days, nor if digoxin or lanatoside C in the previous 4 days; otherwise toxic effects are likely due to persistence of action of the previous doses. If there is doubt about how much to give, a small dose may be given and repeated in a few hours if there is no improvement.

is fairly easy to find in cases of auricular fibrillation where the heart rate is a useful indication of the therapeutic effect. But in congestive cardiac failure the heart rate is not such a useful guide and if the average dose does not produce all the improvement desired, it may be necessary to increase it up to the point of producing toxic effects and then reduce it slightly to ensure that the optimal therapeutic amount is being given. Details of adult dosage are given in the table on p. 290.

Digitalis in Children

Children are considerably less sensitive to digitalis than are adults* but respond equally variably. Perhaps, because few physicians gain the experience with children that is easily acquired with adults, it is safer to use the shorter-acting glycosides. Lanatoside C and digoxin are easier to handle than digitoxin. In children 0 to 5 years a daily total (given in 3 doses) may be calculated as 0·1 mg./Kg., from 5 to 10 years, 0·75 to 1·0 mg. *total* per day; maintenance doses are about one fifth of this.

Toxicity of Digitalis

Toxicity of digitalis was well described by Withering. "The Foxglove, when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, dizziness, confused vision, objects appearing green or yellow . . . slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death." To this may be added headache, cardiac arrhythmias of all sorts (which may cause syncope), but most commonly coupling and extrasystoles, then heart-block, ventricular tachycardia and finally ventricular fibrillation. Bradycardia does not necessarily precede these arrhythmias. It may on occasion be important to distinguish quickly arrhythmias due to digitalis from those due to disease. Abolition by potassium and exacerbation by acetylstrophanthin suggest the former, but the acetylstrophanthin test is dangerous. Mental confusion may occur. Vomiting is principally central, due to stimulation of the chemoreceptor trigger-zone connected to the vomiting centre in the brain.

Milder toxic manifestations require only omission of the drug for an appropriate time. Dangerous arrhythmia may demand administration of potassium chloride orally (5 to 7 G.), which acts in 30 minutes and lasts for several hours. Since toxic effects are liable to return 1 G. potassium chloride may be given orally three times a day subsequently, for a day or two. In desperate circumstances, 1 G. potassium chloride may be given very slowly i.v., provided the pulse and preferably the electrocardiogram are monitored continuously. Too rapid injection is liable to stop the heart. Potassium is dangerous by any route if there is renal failure.

---

* MATHES, S., *et al.* (1952). *J. Amer. med. Ass.*, **150**, 191.

Procainamide and quinidine are not very suitable for treating digitalis-induced arrhythmias as they further increase the block of conducting tissue and the heart may stop, but in emergency it may be necessary to use one of them cautiously.

It may be necessary to withdraw digitalis for up to a week, when it should be recommenced cautiously with very small doses. Allergy to digitalis is extremely rare. Diuretics may precipitate digitalis toxicity by depleting the body of potassium. In a similar way i.v. administration of glucose may induce cardiac arrhythmias in digitalised patients.

Treatment of Congestive Cardiac Failure

The possibility of treating the cause should always be considered, *e.g.* anæmia, thyrotoxicosis, respiratory disease, beri-beri and surgery in suitable cases of mitral stenosis.

In cardiac failure due to myocardial infarction there has been a difference of opinion on whether it is safe to use digitalis, for fear of rupturing the damaged ventricle and of promoting the ventricular arrhythmias which are prone to occur in that condition. The matter is not settled finally but it is probably the lesser risk to use the drug when failure is present or if auricular arrhythmia occurs.

In cardiac failure complicated by arrhythmias the appropriate drug therapy of the arrhythmia is not affected by the presence of the heart failure, except that attempts to convert it to normal rhythm are less likely to succeed.

There has been controversy on the desirability of the use of digitalis in pulmonary heart failure. It is reasonable, at present, to use it.

Acute Severe Congestive Cardiac Failure

1. General: the patient is most comfortable sitting with his legs down in a cardiac bed or armchair. Morphine may be needed to relieve distress; it may cause dangerous respiratory depression in patients with heart failure due to pulmonary insufficiency but is very useful in paroxysmal nocturnal dyspnœa. Constipation, with consequent straining at stool, should be avoided.

2. The patient may be digitalised intravenously and, if very ill, 500 mg. of aminophylline may also be given very slowly i.v. Digitalis is continued by mouth (see table, p. 292). In very severe cases the dose needed to produce maximal therapeutic effect may be only just below or, rarely, just above that which causes serious toxicity.

3. Diuretics play an important part in relieving heart failure. For speed and certainty mersalyl, 2 ml. i.m., gives excellent results, but in most patients oral chlorothiazide is adequate from the start. If mersalyl is used at first, chlorothiazide may be substituted after one or two injections.

4. Acute pulmonary œdema due to hypertension can be treated by hexamethonium, 10 mg. i.v., and repeated as necessary. This reduces the filling pressure of the heart by causing pooling of blood in the periphery. Alternatively venous cuffs on the thighs or actual venesection will give relief. Diuretics are also effective, but less rapidly.

5. A low sodium diet should be begun.

6. Deliberate induction of hypothyroidism with drugs or radio-active iodine has been used in otherwise intractable cases to reduce oxygen requirements.

Milder Congestive Cardiac Failure

The general treatment is the same as for severe cases but is carried out more leisurely. The patient may be digitalised orally (table on p. 290) and oral diuretics used at appropriate intervals with a low sodium diet.

In cases of congestive cardiac failure where the cause is untreatable digitalis will probably be needed for the rest of the patient's life as well as a low sodium diet and occasional use of diuretics. Ion exchange resins might be used.

QUINIDINE

Quinidine is the optical isomer of quinine. Both substances have cardiac and antimalarial effects, but their relative potency differs. The cardiac effect of quinine was observed in 1749 when it was used against "rebellious palpitation," but this was not followed up. In 1912 Wenckebach was visited by a Dutch merchant who wished to get rid of his attacks of auricular fibrillation, which, although they did not unduly inconvenience him, offended his notions of good order in life's affairs. On receiving a guarded prognosis the merchant enquired why there were heart specialists if they could not accomplish what he himself had already achieved. In the face of Wenckebach's incredulity he promised to return the next day with a regular pulse and he did so, at the same time revealing that he had achieved the result by taking quinine. At that time quinine had a reputation as a general remedy rather like that of aspirin today and, taking it empirically, the merchant had found that a gram of quinine would abolish his attacks in about 25 minutes (*4*).

Examination of quinine derivatives led to the introduction of quinidine in 1918.

The way in which quinidine produces its effects is unknown. It is solely a cardiac depressant with the following principal actions:—

Quinidine Depresses the Excitability of cardiac muscle, thus suppressing ectopic pacemakers. This effect is utilised when quinidine is used to stop and to prevent arrhythmias.

Quinidine Prolongs the Effective Refractory Period of cardiac muscle. This action is utilised in converting auricular fibrillation to normal rhythm and in preventing recurrence.

Quinidine Depresses Cardiac Conducting Tissue and prolongs its refractory period; it also depresses the sino-auricular node and slows the speed of impulse conduction throughout the heart. These actions are useful in controlling the heart rate in paroxysmal tachycardias and in stopping arrhythmias.

Quinidine Reduces Vagus Nerve Activity on the heart, like atropine, and therefore protects it from the effects of choline drugs such as methacholine. This antagonism may have clinical importance in causing the failure of choline drugs to arrest severe tachycardias if used in patients taking quinidine. Reduction of vagal tone prolongs the auricular muscle refractory period and so may contribute to the antifibrillatory effect of quinidine.

Other Effects of Quinidine are depression of cardiac contractile force, and hypotension when it is given i.v. (a combination of peripheral vasodilatation and depression of the vasomotor centres and of heart muscle).

Electrocardiographic Changes Due to Quinidine occur with therapeutic doses. The most characteristic effect is prolongation of the Q-T interval due to prolongation of ventricular systole. In addition there may be prolongation of the P-R interval (auriculo-ventricular conduction block), and inversion and prolongation of the T wave.

Absorption and Metabolism of Quinidine

Absorption of quinidine from the alimentary tract is rapid, the action of an oral dose being maximal in about 3 hours and lasting for about 8 hours. Therefore when an increasing effect is required, as in attempts to stop arrhythmias, the drug is given every 2 or 3 hours. If a steady effect is desired doses are usually given 6-hourly when there is slight cumulation for 5 days, after which the effect is constant.

The drug is partly metabolised and partly excreted unchanged in the urine. These processes are slower in patients with cardiac failure.

Uses of Quinidine

Quinidine is used to prevent and to arrest certain arrhythmias and tachycardias. It has no direct beneficial effect in heart failure as it is primarily a cardiac depressant.

Contra-indications to Quinidine are relative; its use is always very much a calculated risk based on sound clinical judgement and knowledge of the drug. Quinidine is especially dangerous in the aged, in patients with severe infections, cardiac damage (e.g. bacterial endocarditis, myocardial infarction, severe valvular disease, auriculo-ventricular conduction defects) or hypersensitivity to the drug.

It is safe, and indeed often desirable, to give quinidine to digitalised patients, but it is dangerous in digitalis intoxication chiefly because of the additive effects of the two drugs on conducting tissue; but quinidine may have to be used to stop digitalis-induced arrhythmias.

Attempts to convert long-standing auricular fibrillation to normal rhythm are undesirable because of the risk of embolism. In addition conversion may be difficult and, when it succeeds, high maintenance doses may be required to prevent recurrence.

Exceptions to all the above contra-indications occur, however.

The decision when to use quinidine could be said to require more skill and experience than any other in drug therapy.

Administration and Dosage of Quinidine

Oral Administration of quinidine sulphate is used except in emergency or when there is vomiting. A test dose (0·2 G.) to reveal the presence of intolerance or hypersensitivity is often recommended, to be given 4 hours before starting a therapeutic course. Digitalisation prior to using quinidine is also recommended by some, but there is only general agreement on the desirability of this in auricular fibrillation and flutter. Some physicians consider both these precautions to be unnecessary, but it is impossible to be dogmatic on either point as the necessary evidence does not exist.

The usual method of giving quinidine to convert an arrhythmia or stop a tachycardia is 0·2 G. 2-hourly, orally, for 5 doses. If this fails each dose is increased to 0·4 G. on the next day, then 0·6 G. and so on. The patient must be closely watched and an electrocardiogram between the 4th and 5th dose is useful in detecting overdosage.

An alternative which may be effective in cases where the 2-hourly régime causes toxic effects is to give quinidine 0·2 G. 6-hourly for 5 days, then 0·4 G. 6-hourly for a further 5 days then 0·6 G., 0·8 G. and so on.

The moment the desired change is achieved the dose is dropped to a maintenance level which is usually about 0·2 G. 3 times a day, although more may be needed. This may be continued for 3 weeks, when it may be stopped to see what happens.

Patients with detectable organic heart disease or frequent attacks of an arrhythmia with an apparently normal heart, commonly need permanent prophylactic administration, but those with mild and infrequent attacks can sometimes do without it even from the moment of conversion. Quinidine should never be continued indefinitely if an arrhythmia is not converted. It then does no good and may interfere with adequate digitalisation.

Quinidine should be stopped if toxic effects more serious than nausea, tinnitus or mild diarrhœa occur, or if the QRS complex on the electrocardiogram exceeds the control value by more than 50% (or 25% if there was initially some prolongation of the QRS), or if frequent (one every 6 seconds) ectopic beats occur.

Toxic effects are common when total dosage exceeds 3 G. in 24 hours.

Intramuscular Administration of quinidine gluconate* is used in patients who are vomiting or when greater haste is desired (maximum action in 1 hour). Two to four injections are given at 2-hourly intervals starting with 0·2 G. and increasing the dose if a further course is needed 24 hours later. If it is not possible to wait 24 hours, the 2-hourly injections may be continued beyond four injections until either a therapeutic or a toxic effect is obtained. This scheme is more dangerous than oral and less dangerous than intravenous therapy, as might be expected. Very close clinical and, if possible electrocardiographic, supervision is essential.

Intravenous Administration of quinidine is rarely needed and as it is very dangerous, is reserved for desperate cases. A solution of 0·6 G. quinidine gluconate is diluted to 50 ml. with 5% glucose and injected over at least 10 minutes. An electrocardiograph should be kept running throughout the injection so that the drug can be stopped immediately on conversion of rhythm or signs of cardiac toxicity (see under oral administration). If an electrocardiogram is not available a second person must feel the pulse continuously. Hypotension is common during i.v. injection so the patient should lie flat if he can; frequent (each minute) blood pressure readings are useful.

If respiratory distress, hypotension, feeble heart sounds or slowing by more than 25 beats/minute occur acutely, the injection is stopped until these effects right themselves (some slowing of the heart will persist) and the injection is then continued, with further interruptions as judged necessary. Conversion may occur up to half an hour after completion of the injection.

What action to take if the injection fails is dubious. Intravenous injection of procainamide is probably best, leaving as long an interval after the quinidine as can be justified by the patient's condition.

Improved results are claimed if quinidine therapy is controlled by frequent estimation of serum levels (*2*).

Toxicity of Quinidine

Cardiac effects vary from ectopic beats to cardiac arrest, or ventricular tachycardia or fibrillation. This effect is perhaps surprising at first sight in a drug which is used to suppress and prevent these irregularities when they are due to other causes. It is suggested, however, that severe depression of the sino-auricular and auriculo-ventricular nodes may cause the heart to develop ectopic foci.

---

* 0·8 G. of the gluconate contains the same amount of quinidine base as 0·6 G. of the sulphate.

Cinchonism occurs as with quinine (p. 79). Hypersensitivity is not rare; rashes, urticaria, angioneurotic œdema, hypotension and collapse, respiratory failure and thrombocytopenic purpura occur. There is sometimes cross-sensitivity with quinine.

PROCAINAMIDE

It has been known for a long time that procaine has quinidine-like actions, but its rapid destruction in the blood as well as its convulsant action, prevented its use as a substitute for quinidine. Study of related substances showed that procainamide is less quickly destroyed than procaine whilst retaining the cardiac and local anæsthetic actions, but having much less central stimulant effect. Electrocardiographic changes are similar to those of quinidine.

Procainamide is well absorbed from the alimentary tract giving a maximum effect in 1 hour (30 minutes, given i.m.). It can also be given i.v. Hypotension and collapse may occur, but they are usually less severe and less prolonged than with quinidine. Other toxic effects are nausea and vomiting, diarrhœa, giddiness and mental depression or hallucinations. Hypersensitivity effects occur, including agranulocytosis. There is cross-sensitivity with procaine.

Contra-indications and precautions during use are the same as those for quinidine. It is sometimes used before and during cardiac operations to prevent arrhythmias.

Dosage and Administration of Procainamide

Doses, as the hydrochloride or sulphate, are given in the table. Auricular arrhythmias may be less sensitive to procainamide than to quinidine and require higher doses than do ventricular. The principle of administration

Dosage of Procainamide in Cardiac Arrhythmias

Route of administration	*Ventricular arrhythmia*	*Auricular arrhythmia*	*Prophylactic maintenance*
Oral	0·5 to 1·0 G. 6-hourly	1·25 G. first dose and then 0·5 to 1·0 G. 2-hourly	0·5 to 1·0 G. 4 to 6-hourly
Intramuscular	0·5 to 1·0 G. 6-hourly		—
Intravenous	100 mg. per minute up to a total dose of 600 mg. or rarely higher		—

is the same as for quinidine, that is, the dosage of the drug is increased until either a therapeutic or a toxic dose is reached.

Choice between Quinidine and Procainamide

Those who regard the two drugs as interchangeable may be right; conclusive evidence does not exist. Procainamide is sometimes said to be less effective therapeutically in auricular than in ventricular arrhythmias, but this may not be true. The advocacy of procainamide for ventricular arrhythmias may well rest in fact on its greater safety in these grave conditions, rather than in greater efficacy. Hypotension during i.v. injection is usually less severe than with quinidine. With either drug, if hypotension is prolonged, phenylephrine 0·5 mg. i.v. may be used to counteract it.

Magnesium Sulphate

Magnesium sulphate given i.v. (15 to 20 ml. of 20% solution in 30 seconds) is a little used treatment of tachycardias and cardiac arrhythmias (5). It should probably be considered only when all more orthodox treatments have failed.

DRUG TREATMENT OF ABNORMALITIES OF CARDIAC RATE AND RHYTHM

Pharmacology of the Cardiac Autonomic Nervous System

Some of the drugs used in heart diseases exert their effects through the autonomic nervous system by mimicking or antagonising the effects of parasympathetic or sympathetic nerves.

The Vagus Nerve (cholinergic, parasympathetic), when stimulated, causes the following effects on the heart:—

a. bradycardia due to depression of the sino-auricular node
b. slowing of conduction in the bundle of His
c. reduced force of contraction of the heart
d. shortening of the refractory period of myocardium
e. decreased myocardial excitability

Some of the effects, *a*, *b*, *d*, and *e*, are used in the therapy of tachycardias and arrhythmias.

The Vagus Nerve may be Stimulated reflexly by various physical manœuvres. These include painful pressure on one or both eyeballs for about half a minute, pressing *one* carotid sinus (the right is said to give better results) for the same time, Valsalva's manœuvre and production of nausea by inviting the patient to put his fingers down his throat. Apomorphine "should be prescribed only by those physicians who have injected this drug into themselves" (*3*).

Vagus nerve endings may be stimulated by drugs which are destroyed less rapidly than acetylcholine (methacholine, carbachol) or by anticholinesterases (neostigmine) which prevent the destruction of the acetylcholine naturally produced at the nerve endings.

The site at which digitalis acts to increase vagal nerve effects is uncertain.

The Vagus Nerve is Blocked by atropine and similar drugs and to some extent by quinidine; these drugs also protect the heart from the effects of choline drugs. Ganglion block reduces vagal activity without, of course, protecting from choline drugs.

The Sympathetic Division of the autonomic nervous system, when stimulated, causes the following effects on the heart:—

a. tachycardia due to stimulation of the sino-auricular node
b. increase in conductivity in the bundle of His
c. increased force of contraction of the heart
d. shortening of refractory period of heart muscle
e. increased excitability of the myocardium

(It may be noted that the effects in the two lists above are not all opposites.)

The only one of these actions used in therapy of heart disease is *b*, when heart-block is treated by ephedrine or other sympathomimetic drugs, and perhaps *c* in severe hypotension due to myocardial infarction. All the sympathomimetic drugs produce these effects to a greater or lesser degree (p. 251).

Ectopic Beats

Ectopic beats very seldom indeed demand drug treatment. When they do, reassurance and sedation (phenobarbitone) are best tried first, but small doses of quinidine (0·2 G. 3 times a day) may be used if these fail.

Paroxysmal Supraventricular Tachycardia

The initial aim is to stimulate the vagus nerve, first by various physical manœuvres. If these fail digoxin i.v. is often effective. Induction of hypertension by phenylephrine may be tried, to induce a vagal depressor reflex. If the attack is very distressing or prolonged, quinidine or procainamide may be used. Prophylactic maintenance therapy may or may not be needed; it is often ineffective. Barbiturate sedation may reduce the frequency of attacks.

In resistant cases choline drugs may be tried provided there is no heart failure. These also act by increasing vagal effects. Methacholine, 15 to 30 mg., is given s.c.; the aged may need more. If the tachycardia does not stop at the height of drug action as shown by flushing (5 minutes), one carotid sinus, never both, may be pressed. The whole process can be repeated 30 minutes later if necessary. A syringe loaded with 2·0 mg. of atropine should be at hand whenever this treatment is given. If excessive bradycardia, hypotension, colic, vomiting or defæcation occur the atropine should be immediately given intravenously. Carbachol 0·25 mg. or neostigmine 1·0 to 3·0 mg. may be given s.c. for the same purpose as methacholine.

If the tachycardia still persists, the patient should be digitalised, if that has not already been done, in an attempt to control the rate. Magnesium sulphate might be tried as a last resort (p. 298).

Paroxysmal supraventricular tachycardia is usually a mild disease and it is well to remember that a patient may suffer more unpleasantness from a retina detached by heavy-handed eyeball pressure (3) or from quinidine or methacholine toxicity, than from the disease.

Paroxysmal Ventricular Tachycardia

Paroxysmal ventricular tachycardia does not respond to vagal stimulation by any method. Quinidine or procainamide are often effective but may induce ventricular fibrillation. Ventricular tachycardia is almost always due to severe organic heart disease. Digitalis, by increasing the excitability of the myocardium, may cause fatal ventricular fibrillation, although if there is severe heart failure its use to control this may be the lesser risk. Magnesium sulphate may be used as a last resort (p. 298).

Auricular Fibrillation

With rheumatic mitral valvular disease it is generally better to control the heart rate with digitalis than to convert it to sinus rhythm. This is because relapse is very common and high prophylactic maintenance doses of quinidine are usually needed. Occasionally there is no tachycardia and no drugs are needed. Where the arrhythmia has been present for less than 6 months it is usually possible to stop it, and the patient often feels better, but there is a risk of causing embolism. Embolism is commoner in long-standing cases where blood clot has formed in the comparatively inactive auricle. The resumption of co-ordinated contraction may detach this clot from the auricular wall with results that range between a few petechiæ and sudden death. In general, contra-indications to conversion are duration of fibrillation of more than 6 months, marked cardiac enlargement or a history of embolism. If cardiac failure is present the failure should be treated before attempting conversion.

"Idiopathic" auricular fibrillation may be continuous or paroxysmal and digitalisation may be followed by resumption of normal rhythm. If not, it can be converted to normal and prevented by quinidine. If relapse is frequent or conversion difficult, it is better simply to control the heart rate with digitalis. Thyrotoxicosis often causes auricular fibrillation which usually reverts to normal rhythm when the patient has become euthyroid.

If it does not, quinidine or procainamide can be used with or without digitalis. In active thyrotoxicosis, should it be necessary to use digitalis, it may not be possible to reduce the pulse rate below 80 minute, without poisoning the patient. Auricular fibrillation due to ischæmic heart disease is best controlled by digitalis as quinidine is more toxic in such cases.

It is often said to be best to digitalise all cases of auricular fibrillation before attempting conversion with quinidine, because the depression of the high rate (500 minute) of auricular contraction with a considerable heart-block, to a lower rate without heart-block may result in a sudden tachycardia which can be disastrous, *e.g.* if 500 impulses per minute come from the auricle and the bundle of His transmits only one out of four (4 : 1 heart-block) the ventricular rate will be 125 minute. When quinidine shows the auricular rate to 200 minute the bundle of His may, despite the effect of the drug in delaying conduction, conduct all the impulses, so that the ventricular rate rises suddenly from 125 to 200 minute. Prior digitalisation appears to prevent this. It is an example of how practical drug therapy cannot be predicted solely from a knowledge of pharmacology. This danger of quinidine had to be discovered in clinical practice.

Auricular Flutter

Auricular flutter is treated by digitalisation, which usually converts it to fibrillation, when the pulse will become irregular. Electrocardiographic control is important as irregularity may also be due to changing auriculo-ventricular block. The fibrillation is then treated as above; high doses are usually needed. Digitalisation alone may restore normal rhythm; if it does not alter the flutter quinidine may be added. Quinidine used alone may result in a sudden tachycardia as in auricular fibrillation. Attacks of flutter may be prevented by prophylactic digitalis or quinidine.

Ventricular Fibrillation (see Cardiac Arrest, p. 302)

Ventricular fibrillation is usually fatal and usually due to severe organic heart disease. It may also be caused by excessive dosage of digitalis, procainamide, quinidine, adrenaline, cyclopropane, trichloroethylene and chloroform. In the case of the three latter the arrhythmia is probably due to the interaction of the drugs and naturally secreted adrenaline on the heart; it therefore follows that adrenaline should *not* be given to patients anæsthetised with these drugs. Noradrenaline is less dangerous in this respect.

If the patient lives long enough, quinidine or procainamide may be used against ventricular fibrillation when it is not due to either drug; the prognosis is bad whatever is done. Surgeons use electric shocks to the heart to stop ventricular fibrillation if it occurs during cardiac operations.

Heart-block

Heart-block does not require treatment unless it is severe enough to cause alterations in consciousness. The auricular rate may be increased by reducing vagal tone with atropine but this can convert partial into complete heart-block and is not recommended.

Sympathomimetic drugs (isoprenaline or ephedrine) may be used to improve conduction. Molar sodium lactate is sometimes successful in cases of multiple Stokes-Adams attacks and may succeed when the above drugs fail. Its mode of action is uncertain. Electrocardiographic control is desirable. 40 to 80 ml. i.v. in 2 minutes is followed by a continuous i.v. infusion at 60 to 150 drops/minute. As the ventricular rate increases the infusion is slowed and eventually stopped. Molar lactate may also be used in cases of cardiac arrest and is an effective antidote to the cardiac effects of a raised serum potassium. Ectopic rhythms may arise during infusion, especially in patients who had ectopic beats before treatment. Heart failure may develop (*6*).

If congestive heart failure is present with heart-block, digitalis may be used and therapeutic effects achieved in doses which do not increase the heart-block. There is, however, a possibility of making the block complete. If block is already complete digitalis may be used freely.

Stokes-Adams Attacks may be due to cardiac arrest, ventricular tachycardia or fibrillation, and some aspects are considered above. It is doubtful whether intracardiac injections are helpful in the treatment of such cardiac arrest, especially of adrenaline, which can cause ventricular fibrillation. "The best treatment consists of mechanical stimulation of the heart by punching the chest vigorously with the fist" (*3*). An electrical shock can be used (artificial pacemaker).

CARDIAC ARREST

Cardiac arrest that is not due primarily to cardiac disease is sometimes treated by massage of the organ to maintain the circulation to the brain until the heart can be persuaded to resume independent function. The details of cardiac massage are inappropriate to this book, but drugs are sometimes needed to restore tone and spontaneous beat.

If the heart shows no sign of recommencing soon after massage has begun, 5 ml. of 10% solution of calcium chloride may be injected into the left ventricle and, if this is not followed by resumption of beat, 2–5 ml. of a 1 in 10,000 solution of adrenaline (adrenaline B.P. is 1 in 1,000) may also be injected into the same site.

If ventricular fibrillation occurs, electrical defibrillation will be required after myocardial tone has improved under the influence of the injections.

Numerous other schemes for treating cardiac arrest have been proposed. Controlled trials are, not surprisingly, lacking. Calcium has effects like digitalis and increases cardiac "tone" (p. 286) which is useful if the heart is very relaxed and flabby, for massage is less effective, the blood merely being squeezed from one part to another, with less ejection into the great arteries.

Guide to Further Reading

On Digitalis

(*1*) Peck, T. W., and Wilkinson, K. D (1950). William Withering of Birmingham. Bristol: John Wright.
(*2*) Dimond, E. G. (1957). Editor. Digitalis. Springfield: Thomas.
(*3*) Gold, H. (1959). Experiences in human pharmacology. *In* Quantitative Methods in Human Pharmacology and Therapeutics. Ed. D. R. Laurence. London: Pergamon Press.
(*4*) Lown, B., and Levine, S. A. (1954). Current concepts in digitalis therapy. *New Engl. J. Med.*, **250**, 771, 819, 866.
(*5*) Lown, B., and Levine, S. A. (1955). Current Concepts in Digitalis Therapy. London: Churchill.
(*6*) Conference on Therapy (1957). Selection of digitalis preparations and their proper administration. *Amer. J. Med.*, **17**, 271.
(7) Editorial (1953). Primitive poisons. *Lancet*, (*i*), 1036.
(*8*) Bing, R. J., *et al.* (1951). Myocardial oxidative metabolism and initial fibre length of the failing human heart. *J. clin. Invest.*, **30**, 630.
(*9*) Burch, G. E., Ray, C. T., and Cronvich, J. A. (1952). Certain mechanical peculiarities of the human cardiac pump in normal and diseased states. *Circulation*, **5**, 504.

On Other Drugs Used in Cardiac Arrhythmias

(*1*) Gold, H. (1950). Quinidine in Disorders of the Heart. New York: Hoeber.
(*2*) Sokolow, M., and Ball, R. E. (1956). Factors influencing conversion of chronic atrial fibrillation with special reference to quinidine concentration. *Circulation*, **14**, 568.
(*3*) Scherf, D. (1953). Treatment of cardiac arrhythmias. *Circulation*, **8**, 756.
(*4*) Wenckebach, K. F. (1923). Cinchona derivatives in the treatment of heart disorders. *J. Amer. med. Ass.*, **81**, 472.
(*5*) Boyd, L. J., and Scherf, D. (1943). Magnesium sulphate in paroxysmal tachycardia. *Amer. J. med. Sci.*, **206**, 43.
(*6*) Bellet, S., and Wasserman, F. (1957). Indications and contra-indications for the use of molar sodium lactate. *Circulation*, **15**, 591.

Chapter 17

DIURETICS

Any substance which increases urine production can be said to be a diuretic but this wide definition includes many drugs not commonly thought of as such. For instance, when digitalis is given to a patient in congestive cardiac failure there is usually a diuresis, and alcohol is an effective diuretic though it is never used as such in therapeutics; everyone has personal experience of the diuretic properties of water. To be therapeutically useful a diuretic should increase the output of sodium as well as of water.

Diuretics may or may not act directly on the kidney. Normally about 99% of the water filtered across the glomeruli is reabsorbed by the renal tubules. Therefore, to double the rate of urine production, tubular reabsorption remaining constant, the glomerular filtration rate would have to double; if, however, the glomerular filtration rate remains constant then a reduction of only about 1% in tubular reabsorption will double the output of urine. The diuretics that are used clinically and which act directly on the kidney, affect the tubules rather than the glomeruli.

Diuresis may be initiated:—

OUTSIDE THE KIDNEY:—

a. By inhibiting the release of antidiuretic hormone, *e.g.* water, hypotonic solutions, alcohol.

b. By raising the cardiac output and increasing renal blood flow, *e.g.* digitalis in cardiac failure.

c. By mobilising peripheral œdema fluid, *e.g.* albumen in hypoproteinæmic states, and sodium restriction, either dietary or with ion exchange resins in addition.

BY DECREASING REABSORPTION BY THE RENAL TUBULES:—

a. By osmosis, *e.g.* urea.

b. By reducing the reabsorption of electrolytes, *e.g.* organic mercurials, chlorothiazide, acetazolamide, aldosterone antagonists.

Assessment of Diuretics

It is possible to decide if a substance is an effective diuretic by giving it to œdematous patients and measuring weight change and changes in sodium and water output; the incidence of side-effects is taken into account, of course, in deciding whether the drug is likely to be useful. Although this sounds simple enough there are a number of practical difficulties,[*] and an accurate comparison of two diuretics is seldom possible in severely œdematous bed-ridden patients because their condition changes so rapidly. A comparison can, however, be made very elegantly in a group of relatively stable ambulant œdematous cardiac patients.[†] It is obviously not justifiable to assume that the result will necessarily hold in œdema of other ætiology, but in fact there is little or no difference in the relative efficiency of the various diuretics in the many different types of œdema.

Measurement of Weight Changes is the simplest guide to the success or failure of diuretic régimes. Intake and output charts are a more complicated, and often less accurate, alternative.

Salt and Water Restriction

Sodium Restriction

Abnormal retention of sodium occurs in œdematous patients and the excess extracellular fluid (*i.e.* œdema) cannot usually be retained if its sodium concentration is lowered. Clinically useful diuretics increase the excretion of sodium, but this will only lead to mobilisation of œdema fluid if its replacement by sodium from the diet is prevented. Dietary sodium restriction is thus an important part of all potent diuretic régimes. A normal diet contains about 10 G. of sodium chloride a day (1 G. of sodium chloride contains about 170 mEq. of sodium). If no salt is added in cooking or at mealtimes this may fall to about 3 to 5 G. a day. This is often not low enough and so special low-salt diets (about 1 G. daily) are given. Really extreme salt restriction, as with rice diets, is not usually tolerated by the patient and is seldom necessary. Some patients find various mixtures of potassium salts helpful as "salt substitutes," lithium salts were used in the past but are too toxic.

Occasionally homeostasis becomes so grossly deranged as to allow œdema to be present together with an abnormally low concentration (below 130 mEq./litre) of sodium in the extracellular fluid and plasma. This syndrome sometimes follows excessive sodium depletion in œdematous patients and is a hazard common to all effective diuretic régimes. It is accompanied by weakness and malaise. The total body sodium is often normal or increased in this syndrome, but is diluted with a gross excess of water. Sodium restriction and use of diuretics must be stopped at least temporarily, but for some unknown reason, possibly connected with abnormalities of electrolytes within the cells, the administration of extra salt, or hypertonic saline, often only expands the extracellular fluid still further without restoring the sodium concentration to normal. Occasionally such patients respond to extra potassium or to hydrocortisone with saline i.v. Treatment is frequently ineffective.

---

[*] Spencer, A. G., and Lloyd-Thomas, H. G. (1953). *Brit. med. J.*, (*i*), 957.

[†] Greiner, T. H. (1957). *Ann. N.Y. Acad. Sci.*, **65**, 604.

Water Restriction

Moderate fluid restriction is recommended by some as part of diuretic régimes, but is certainly not as important as salt restriction. Strict fluid deprivation merely causes intolerable thirst.

Organic Mercurial Diuretics

The organic mercurials have been the most widely used diuretics for the last 30 years. The diuretic power of an organic mercurial was first discovered in Vienna when merbaphen (Novasurol) was tried as an antisyphilitic in a ward where the measurement of urine output was part of the nursing routine. Merbaphen, although unsatisfactory as an antisyphilitic, was then given to many œdematous patients, in whom it proved to be an effective diuretic, but it was very toxic and was soon replaced by mersalyl. A host of organic mercurial diuretics are now available.

The Action of Organic Mercurial Diuretics on the kidney is probably to inhibit chloride reabsorption in the proximal renal tubules. Thus a chloride diuresis occurs which is necessarily accompanied by an equivalent diuresis of cations, mainly sodium and potassium, and of water. The loss of chloride in the acid urine is compensated for by carbon dioxide retention, with a raised serum bicarbonate level, so that a hypochloræmic alkalosis results. Chloride deficiency may thus prevent maximal diuresis, and can be avoided by routinely giving ammonium chloride (1 to 2 G. orally on the morning of the injection) whenever organic mercurial diuretics are used.

The inorganic salts of mercury are effective diuretics but the mercury ions are very toxic to the tissues through which they must pass before they get to the kidneys. The great advantages of the organic compounds of mercury are firstly that organically bound mercury is much less toxic, and secondly that the organic mercurials are rapidly excreted through the kidneys. The hypothesis that a small proportion of the organic mercurial is broken down in the kidney and that the mercuric ions so liberated produce the diuresis is probably untrue; it is not known how the mercury blocks chloride transport.

Uses of Organic Mercurial Diuretics. They are mainly used in patients with œdema due to heart failure. They may be used cautiously in other forms of œdema (but not that of acute nephritis). In heart failure complicating renal failure very great caution is obviously essential and some would say mercurials are contra-indicated.

Preparations, Dosage and Routes of Administration of the Organic Mercurial Diuretics. They are best given intramuscularly because intravenously they occasionally cause cardiac arrhythmia or arrest, and subcutaneously they often cause painful tissue necrosis. Some organic mercurials have been developed especially for oral use, for instance chlormerodrin; they are less reliable than mercurials given parenterally and they often cause nausea, vomiting, diarrhœa and abdominal pain, although these may also occur after injections of mercurials. Those developed for subcutaneous injection, for instance mercaptomerin sodium, are less irritant than mersalyl but the injections are still painful and cause an occasional local reaction.

Mersalyl Injection, B.P., is a solution of a mersalyl-theophylline complex, 1 ml. contains 40 mg. of mercury and 50 mg. of theophylline. This small amount of theophylline has no significant diuretic effect, but the complex is better absorbed from the injection site than is mersalyl alone. The initial dose is 1 ml. and it is desirable to ask patients whether they have been made ill by mersalyl in the past. The diuresis usually begins within 3 hours of the i.m. injection, is maximal at about 7 hours, but some effects may persist for over 24 hours. Therefore if sleep is to be undisturbed, organic mercurial diuretics should be given early in the morning. 1 to 2 ml. of mersalyl are given on alternate days for the first 2 doses and then once or twice a week; larger doses are usually no more effective but are more toxic. If there is still no diuresis after the third dose, the drug should be stopped. Patients can only occasionally be taught to give their own intramuscular, as opposed to subcutaneous, injections.

Toxic Effects of Organic Mercurial Diuretics, in addition to those already mentioned, include hypersensitivity reactions of various kinds, particularly fever and rashes. Sudden death from ventricular fibrillation may follow i.v. injection of organic mercurials and in any case the increased efficacy of i.v. injection is trivial. Chronic toxic effects resemble those of inorganic mercury poisoning and include renal damage (blood, protein and casts in the urine), stomatitis and liver damage. They are very rare when proper doses are used. A sudden increase in urine output may precipitate acute retention of urine in elderly men with prostatic enlargement. The syndrome associated with a low concentration of sodium in the extracellular fluid may be precipitated. The temporary hypochloræmic alkalosis necessarily induced when organic mercurials are exerting their diuretic effect does no harm and it is rare for sufficient potassium to be lost in the urine to cause symptoms of potassium deficiency.

Since organic mercurial diuretics are excreted through the kidneys they should be used with great caution in patients with any renal disease and never in acute nephritis.

Chlorothiazide

Chlorothiazide (Saluric) was introduced in 1957. It is the first powerful and reliable oral diuretic and is therefore an important advance in drug therapy. It is a synthetic organic compound and contains no mercury. Its main action is to depress renal tubular reabsorption of sodium, potassium and chloride, but it is also a feeble carbonic anhydrase inhibitor.

Chlorothiazide potentiates hypotensive drugs and also has a hypotensive action on its own account. This effect may be due to reduction in plasma volume, and to a direct effect on blood vessels.

Chlorothiazide can be used in all forms of œdema apart from that of acute nephritis. The dose is 0·5 to 1 G. orally, twice a day, before breakfast and after lunch (to avoid disturbing sleep). For short-term use this may be repeated on, say, three successive days, but for chronic use it is given on 1 to 3 non-consecutive days a week. Intermittent administration is preferable because of the considerable urinary loss of potassium, and supplementary potassium should always be given whenever chlorothiazide is used. 2 to 4 G. of potassium chloride is usually given on the same day as the chlorothiazide but is probably more effective in preventing potassium depletion if given on a different day from the diuretic. Some patients seem to need larger potassium supplements than this. A chlorothiazide preparation for i.v. use is available but rarely required.

Toxic effects of chlorothiazide are uncommon, apart from potassium deficiency which may lead to digitalis toxicity in cardiac patients and neuropsychiatric symptoms in patients with hepatic disease. The drug has not yet been in general use for long enough to assess long-term toxicity; rashes, thrombocytopenic purpura and agranulocytosis have been reported. As with all effective diuretics, the syndrome associated with a low concentration of sodium in the extracellular fluid may be precipitated, as may acute retention of urine in elderly men. If chlorothiazide is used continuously some patients can be kept free from œdema even if their sodium intake is allowed to increase, so that they may be able to change from a "low salt" to a "no added salt" diet. It is not yet certain that long-term use of this drug is sufficiently safe for this to be justifiable.

Hydrochlorothiazide has been introduced more recently; it does not differ significantly from chlorothiazide pharmacologically except that it is a weaker carbonic anhydrase inhibitor so that there is less bicarbonate excretion, but its greater potency means that smaller tablets can be used. The dose is 50 to 100 mg. orally twice a day. Tablets containing hydrochlorothiazide plus a small dose of potassium is available.

Hydroflumethiazide and bendrofluazide are similar to hydrochlorothiazide; both cause potassium loss in the urine.

Acetazolamide

Acetazolamide (Diamox) is a sulphonamide which inhibits the enzyme carbonic anhydrase and is of greater experimental and theoretical than therapeutic importance. Several sulphonamides are known to be weak carbonic anhydrase inhibitors, and acetazolamide was discovered during a systematic search for a more effective inhibitor of the enzyme.

Carbonic anhydrase facilitates the reaction between carbon dioxide and water to form carbonic acid:—

$$CO_2 + H_2O \xrightleftharpoons{\text{carbonic anhydrase}} H_2CO_3 \rightleftharpoons H^+ + HCO_3'$$

the reaction being slow in the absence of the enzyme. The carbonic acid is, of course, in equilibrium with its dissociation products, hydrogen and bicarbonate ions. Carbonic anhydrase is present in high concentration in the erythrocytes, where it speeds up carbon dioxide transport. The reaction is also fundamental to the production of either acid or alkaline secretions and a high concentration of carbonic anhydrase is present in the gastric mucosa, pancreas and kidney. In the kidney, for instance, the function of carbonic anhydrase is to provide hydrogen ions to be exchanged for sodium in the glomerular filtrate, so that body sodium is conserved.

Hydrogen ions are secreted by the tubular cells into the glomerular filtrate as it passes along the renal tubules. Sodium ions enter these cells from the filtrate in exchange for the hydrogen ions. Thus H_2CO_3 is formed in the filtrate and $NaHCO_3$ in the tubule cells. The H_2CO_3 dissociates to form CO_2, which probably diffuses passively into the cells, and H_2O. The $NaHCO_3$ is passed from the cells into the extracellular fluid.

This reabsorption of sodium in exchange for hydrogen ions can only continue so long as there is a good supply of hydrogen ions, and this depends upon the action of carbonic anhydrase. Inhibition of the enzyme reduces the supply of hydrogen ions and so the sodium and bicarbonate remain in the renal tubular lumen. Thus an alkaline urine with a high sodium and bicarbonate content results. The increase in sodium excretion leads to a diuresis. Potassium excretion is also increased by acetazolamide, but the details are not understood.

The excretion of an alkaline urine makes the extracellular fluid more acid. Carbon dioxide is blown off through the lungs to compensate, leading to a reduction in the plasma bicarbonate, *i.e.* a metabolic acidosis results. The reduction in the plasma bicarbonate necessarily reduces the amount of sodium bicarbonate in the glomerular filtrate. If repeated doses of acetazolamide are given this fall in the amount of sodium bicarbonate presented to the renal tubules continues until the level is reached at which the sodium can be reabsorbed by exchange with the relatively slow supply of hydrogen ions which are available even though carbonic anhydrase is inhibited. A new equilibrium is thus set up in which there is a metabolic acidosis but in which the sodium and water diuresis stops.

Therefore acetazolamide is only effective as a diuretic if given intermittently so as to allow the plasma bicarbonate to be restored before the next dose; if given 8-hourly diuresis usually stops after the second dose. It is therefore usual to give a single dose of 250 or 500 mg. orally on alternate days. Maximal diuresis occurs in the first 8 hours after a single dose but it is very ineffective compared with mersalyl or chlorothiazide, and it often fails.

Acetazolamide is sometimes used to supplement mersalyl, but usually on a different day. Mersalyl produces a metabolic alkalosis and so alternation with acetazolamide minimises the acid-base disturbance; in some patients control of œdema is improved.

Toxic effects of acetazolamide are uncommon; high doses may cause drowsiness and paræsthesiæ may occur, blood dyscrasias have been reported. It is not used in liver failure as it has occasionally precipitated hepatic coma.

Excretion of the ganglion-blocking drugs is delayed if the urine is alkaline, so they may be potentiated by acetazolamide. The inhibition of carbonic anhydrase in sites other than the kidney produces few significant effects. Acid secretion in the stomach is reduced, but not enough to be useful in the treatment of peptic ulcer.

Ketogenic diets have been used in epilepsy to produce a metabolic acidosis which was thought to reduce the frequency of fits. Acetazolamide was therefore tried to see if the resulting acidosis was therapeutically useful; also there is much carbonic anhydrase in the brain. Despite initial enthusiasm the results of careful trial are disappointing.

Acetazolamide is used to relieve glaucoma, but the mechanism is obscure. An alternative is dichlorphenamide (Daramide).

Ammonium Chloride

Ammonium chloride is a weak diuretic, but is used to provide the adequate supply of chloride ions which are essential for a maximal response to the organic mercurials. After the ammonium chloride is absorbed it is converted into urea, and hydrochloric acid which is buffered mainly by sodium bicarbonate, *e.g.* $NaHCO_3 + HCl = NaCl + H_2CO_3 = CO_2 + H_2O$. Thus a metabolic acidosis, with low plasma bicarbonate and high chloride, results. The excess chloride is excreted by the kidney in an acid urine, and the main use of ammonium chloride given alone is to make the urine acid. However, the acidosis stimulates the kidney to produce ammonium and after a few days' constant administration, the kidney excretes as much ammonium chloride as most patients are willing to take. Ammonium chloride by itself is thus only effective as a diuretic if given intermittently; only a small diuresis results from 8 to 12 G. daily in divided doses. This high dose causes gastric irritation, abdominal pain, nausea and vomiting, and any dose may be dangerous in patients with poor renal function, whose kidneys may be unable to produce ammonia, and although a diuresis may result it may be at the expense of a severe uncompensated acidosis.

Xanthine Diuretics

The general properties of the xanthines (theophylline, theobromine, caffeine) are discussed on p. 225. These compounds are weak diuretics and are useless for this purpose in therapeutics. They act in an unknown way, inhibiting absorption of sodium and water in the renal tubules to produce a small diuresis.

Amino-uracil Diuretics, aminometradine (Mictine) and amisometradine (Rolicton) are relatively feeble diuretics which have never gained wide use because chlorothiazide appeared soon after their introduction.

Ion-exchange Resins (*1*)

Ion-exchange resins are insoluble aggregates of macromolecules which contain acidic (cation-exchange) or basic (anion-exchange) groups.

Cation-exchange Resins ionise like acids even though they are insoluble. They are used to withdraw sodium or potassium from the body. Each gram of resin will increase the fæcal sodium by about 1 mEq. If the resin is given orally in the hydrogen-, ammonium- or potassium-form, these ions will exchange mainly for sodium ions high in the gastro-intestinal tract, because the concentration of sodium ions there is greater than that of other cations. However, the resin has a greater affinity for calcium and potassium than it has for sodium and therefore, as it passes down the intestine, an increasing amount exchanges to the calcium- and potassium-forms, liberating the sodium which is reabsorbed into the body again. The amount of sodium-form resin passing out in the fæces is greater when passage of the resin through the intestine is fast. Therefore laxatives are often given with cation-exchange resins, but obviously the laxative should not contain cations.

If the resin is given entirely in the ammonium-form a potassium deficiency state may result which is particularly dangerous in digitalised patients. A metabolic acidosis (low plasma bicarbonate) is also likely to be produced because ammonium-form resin is equivalent to ammonium chloride in this respect, but unless very severe it does no harm and increases the output of sodium in the urine. Calcium deficiency may occur. To minimise the hypokalæmia the resins are usually given partly in the potassium- and partly in the ammonium-forms; the hydrogen form cannot be used because it has a burning very acid taste. It is usual to give 20 to 60 G. of resin (*e.g.* Katonium, in which 75% is in the ammonium- and 25% in the potassium-form) daily in divided doses on 5 days a week, and to supply extra potassium (2 to 5 G. of potassium chloride daily) for 2 days at weekends. The resins feel like sand in the mouth; they are usually swallowed as a suspension in water or in cachets.

The resins lead to a significant diuresis only when the patient is on a strict low-salt diet. They are sometimes given to prevent œdema re-accumulating in patients who will tolerate only moderate sodium restriction.

Ion-exchange resins are used in the nephrotic syndrome, or combined with other diuretics in the treatment of cardiac œdema. They may be used cautiously in œdema due to cirrhosis of the liver, but the ammonium-form, like any ammonium salt, may precipitate acute hepatic failure. Sodium-form resins (Resonium-A) are used in potassium intoxication to withdraw potassium from the body, and can be given in retention enemata as well as by mouth.

Anion-exchange Resins have been used to reduce gastric acidity in peptic ulceration but are unpleasant to take and have no advantages over the more usual antacids. They are not diuretics.

Osmotic Diuretics

Any substance which passes across the glomerular membrane and which is not completely reabsorbed in the renal tubules necessarily has some diuretic effect. Water is retained within the renal tubule by osmosis and so the volume of urine increases. The excretion of electrolytes is also increased, partly because the increased rate of flow down the tubules does not allow as much time for reabsorption, and partly because withdrawal of water from the body must be accompanied by electrolyte excretion to maintain homeostasis. Osmotic diuretics have little place in therapeutics, but a good example of an osmotic diuresis is that due to glucose in diabetes mellitus.

Urea. If urea is given to the patient the amount filtered will increase. The blood urea is necessarily raised, but this is not in itself usually of any importance. The amounts of urea required to obtain a satisfactory diuresis are large (15 to 20 G. orally 2 to 5 times a day). In the majority of patients such doses cause nausea and sometimes vomiting even if the unpleasant taste is disguised with fruit juices or syrup. However, a few chronically œdematous patients will tolerate it, and in them urea can be a useful maintenance diuretic.

Mannitol and Inulin are carbohydrates which are filtered across the glomeruli, but not reabsorbed to any significant extent in the tubules. They have to be given by i.v. infusion and are of little use as diuretics. Their chief importance is in experimental medicine for the measurement of the glomerular filtration rate.

Sucrose given by mouth is split into glucose and fructose before absorption, but an i.v. injection of 50% sucrose, which is very hypertonic, temporarily expands the volume of circulating fluid by drawing fluid out of the tissues and extravascular spaces. It is used for this purpose to lower the intracranial pressure. 50 to 100 ml. are given and repeated according to the response. The effect is only transient and triple strength plasma is probably more satisfactory. Sucrose i.v. also acts as an osmotic diuretic but is not used for this purpose as it is so transient and because large amounts damage the renal tubules, although this is reversible.

Dextrose (glucose). A 50% solution of glucose can be used i.v. instead of sucrose in the treatment of cerebral œdema, but the effects are even more transient as glucose is a smaller molecule which enters the cells faster and is metabolised rapidly.

The osmotic diuretic effect of glucose is responsible for much of the sodium and water loss in diabetic ketosis but it is not used therapeutically as a diuretic.

Aldosterone Antagonists

Steroid Spirolactones, of which spironolactone (Aldactone) is one, are competitive antagonists of action of aldosterone on the renal tubule. Aldosterone causes sodium retention, and potassium loss in the urine, and contributes in part at least to the œdema of congestive heart failure, hepatic cirrhosis and the nephrotic syndrome, in which conditions increased aldosterone production has been found.

In some resistant cases of œdema spironolactone, used in conjunction with chlorothiazide and/or mersalyl, may result in a diuresis where the latter two used alone have failed.

Choice of Diuretic

It is sometimes possible to treat the cause of the œdema and this should always be done if possible.

Chlorothiazide is probably the diuretic of choice in most œdematous patients and can be given i.v. where injection is preferred for the greater certainty that it provides over oral administration. However, the organic mercurial diuretics have been in effective use for many years and mersalyl, i.m., is commonly used initially in urgent cases.

Large accumulations of ascitic fluid or pleural effusions are often removed by tapping, partly for the sake of speed and partly because diuretics are more effective in preventing fluid re-accumulating in the body cavities than in removing it once a large effusion has formed. Ascitic fluid contains relatively large amounts of protein and repeated paracenteses may aggravate hypoproteinæmia. Southey's Tubes may be used to drain fluid from the legs in patients with obstinate œdema, but this is seldom necessary nowadays and can seriously deplete the patient of sodium. Any vigorous diuresis may precipitate an attack of gout in patients subject to that disease.

Failure of Diuretic Therapy

Œdema sometimes persists despite the most vigorous diuretic régimes. This is most common in the terminal phase of an illness when homeostasis is grossly deranged, but the cause of failure can sometimes be removed.

In Severe Congestive Cardiac Failure the cardiac output, and hence the glomerular filtration rate, may be so low that the renal tubules can easily reabsorb nearly all of the sodium and water presented to them. The glomerular filtration rate must be improved before any diuretic is likely to be successful and so, in addition to digitalising the patient, it is reasonable to give 500 mg. of aminophylline by slow i.v. injection 2 hours after mersalyl or chlorothiazide in resistant cases.

In Severe Abnormalities of Electrolyte Distribution, especially when there is a low concentration of sodium in the extracellular fluid, diuretics seldom work. It is obviously desirable to restore normality, but this can be difficult. More specific and less serious electrolyte disturbances may account for the failure of certain diuretics in certain patients, e.g. organic mercurial diuretics are likely to fail if there is hypochloræmia.

GUIDE TO FURTHER READING ON DIURETICS

(*1*) SPENCER, A. G., and LLOYD-THOMAS, H. L. G. (1954). A critical analysis of cation-exchange therapy. *Brit. med. J.*, (2), 597.

(*2*) Reports of a conference on chlorothiazide and other diuretic agents (1958). Ed. J. V. Taggart. *Ann. N.Y. Acad. Sci.*, **71**, 323.

(*3*) FORD, R. V. *et al.* (1958). Choice of a diuretic agent based on pharmacologic principles. *J. Amer. med. Ass.*, **166**, 129.

(*4*) BERLINER, R. W., and ORLOFF, J. (1956). Carbonic anhydrase inhibitors. *Pharmacol. Rev.*, **8**, 137.

(*5*) GREINER, T., *et al.* (1953). The value of ammonium chloride as an adjuvant to the mercurial diuretics determined by a bioassay in patients with congestive failure. *J. Pharmacol. exp. Ther.*, **108**, 481.

(*6*) PITTS, R. F. (1960). The Physiological Basis of Diuretic Therapy. Oxford: Blackwell.

Chapter 18

ANTACIDS, PURGATIVES, CONSTIPATION AND DIARRHŒA

GASTRIC ANTACIDS

Substances which reduce gastric acidity by adsorbing or chemically combining with hydrochloric acid may be divided into two groups. The first comprises substances which are absorbed and are capable of altering the acid-base balance of the body, the *Systemic Antacids*. The second contains substances which are little absorbed or not absorbed and which do not significantly alter the acid-base balance of the body, the *Non-Systemic Antacids*. Food, especially milk, can be regarded and used as an effective non-systemic antacid.

Systemic Antacids

The principle systemic antacids are sodium and potassium bicarbonate; they relieve pain quicker than any other antacids, but also for a shorter time. The citrates are used in various effervescent preparations. These substances release carbon dioxide in the stomach and this may cause discomfort and belching, which latter may have a psychotherapeutic effect or not, according to circumstances. There is no sound clinical basis for the concept of "rebound" acid secretion due to a stimulant effect of the carbon dioxide on acid secretion. Sodium and potassium citrate are commonly used to make the urine alkaline. There are mixtures for the purpose in the B.N.F.

Non-Systemic Antacids

Aluminium Hydroxide reacts with hydrochloric acid in the stomach to form aluminium chloride which reacts with intestinal secretions forming insoluble salts, especially phosphate, the chloride being released and reabsorbed. Aluminium hydroxide can be used in patients who habitually form phosphatic urinary calculi to increase fæcal, and decrease renal, phosphate excretion, but enormous amounts are needed. In addition to neutralising acid, aluminium hydroxide inactivates pepsin. It tends to constipate. Kaolin (aluminium silicate) may also be used as an antacid to act by adsorption.

Magnesium Trisilicate reacts with hydrochloric acid in the stomach to form magnesium chloride which reacts with intestinal secretions to form the carbonate, the chloride being released and reabsorbed. Like all magnesium salts it tends to cause diarrhœa by acting as a bulk purgative. It adsorbs pepsin.

Magnesium Oxide and Carbonate are also used, the latter releasing carbon dioxide in the stomach.

Calcium Carbonate and Hydroxide are used similarly. They tend to constipate and if used in excess, especially when combined with a milk diet, enough may be absorbed to cause the hypercalcæmic syndrome (headache, weakness, anorexia, nausea and vomiting) with temporary, or rarely permanent, renal damage.

Preparations and Uses of Antacids

The number of antacid preparations available is huge and includes substances not mentioned above, but which have no proved advantages. It is obviously preferable to use non-systemic antacids, and aluminium hydroxide or magnesium trisilicate or a mixture of the two adjusted to suit the patient's bowel function, will give results not less satisfactory than any other. A combination of calcium and magnesium carbonates will also serve. Aluminium and calcium salts constipate and magnesium salts cause diarrhœa. They may be taken as tablets, which should be crushed or chewed, as powder or as liquid suspensions.

Magnesium Trisilicate Compound Tablets, B.N.F., contain magnesium trisilicate (260 mg.) and dried aluminium hydroxide gel (130 mg.), the dose is 1 to 2 tablets.

Sodium Bicarbonate Compound Tablets, B.P., contain 325 mg. sodium bicarbonate. The dose is 1 to 2 tablets.

A comprehensive list of gastric antacid preparations will be found in the B.N.F. Bismuth salts are obsolete.

In severe cases antacids may be administered 2-hourly with small feeds or included in a continuous gastric milk infusion. Continuous sucking of antacid tablets is especially useful, for perhaps the chief factor preventing effective neutralisation of gastric acid is the rapid passage of the antacid into the duodenum, so that intermittent administration fails to achieve its aim. Continuous sucking is especially useful in reflux œsophagitis. In milder cases antacids are given after meals, on going to bed and whenever the patient feels pain.

Mechanical effects, *i.e.* coating the stomach wall to afford protection, are probably insignificant even if they occur.

Alkalosis can, when it happens, cause confusion in diagnosis. Prevention is best accomplished by awareness of the possibility of its occurrence. Alkalosis solely due to absorption of alkali seldom causes symptoms in the absence of renal or circulatory failure. Patients have been kept in severe alkalosis with sodium bicarbonate for 3 weeks without significant symptoms, although the possibility of renal damage is not excluded in more prolonged alkalosis.

But alkalosis due to loss of chloride in vomit is accompanied by dehydration and renal ischæmia and gives rise to severe symptoms. Both kinds may be present simultaneously. Reduction in ionised calcium in alkalosis may result in tetany.

PEPTIC ULCER

A complete account of the medical treatment of this disease involves a great deal more than the mere use of drugs and is outside the scope of this book, but it may be summarised thus:—

1. General management of life which may include sedation (phenobarbitone).
2. Bed rest in severe cases.
3. Diet; small frequent meals, avoiding foods the patient knows by experience to be followed by pain.
4. Antacids (magnesium trisilicate, aluminium hydroxide).
5. Antisecretory or anticholine drugs (propantheline).
6. Inactivation of pepsin by adsorption (magnesium trisilicate) or by chemical action (aluminium hydroxide).

It might be supposed that diet and antacids, which give such great symptomatic relief in peptic ulcer, would also promote healing and prevent relapses, but this is not so. Bed rest and cessation of smoking, however, do have these desirable effects (*3, 4, 5, 6*).

The principal objective of drug therapy is the elimination of hydrochloric acid to raise the pH of the gastric contents and so abolish peptic activity (*1*). Since no drug is capable of this, used alone, the ideal must be approached in a number of ways:—

First by the avoidance of substances which provoke gastric acid secretion or irritate the mucous membrane. These include alcohol and tobacco, excess of tea or coffee, adrenocortical steroids and corticotrophin, salicylates, phenylbutazone and reserpine. (When these drugs must be used, antacids can be given with them.)

Second by the neutralisation of acid in the stomach by antacids which can be taken intermittently as a mixture or powder after food and at night, or nearly continuously by sucking tablet after tablet all day. There is no way of neutralising acid all night, other than by waking up and taking a drug or food, or having a continuous intragastric infusion.

The purpose of using anticholine drugs is to reduce gastric secretion, and also muscular spasm, by blocking nervous pathways. Muscle spasm is a nebulous concept which can be imagined more easily than it can be demonstrated experimentally. The reduction in motility may be advantageous in delaying gastric emptying, and so allowing food to neutralise more acid, but disadvantageous in that it prevents mixing of antacids with gastric contents and because it can lead to functional pyloric obstruction if there is already organic pyloric stenosis. It is hoped that the use of anticholine drugs may enable good results to be obtained with a less rigid dietary and antacid régime, and this prospective freedom from restrictions is one reason for their popularity. Atropine is not very effective at tolerable doses, and many synthetic drugs are even less useful. Propantheline is probably the best for general use followed by hyoscine methobromide and penthienate bromide. They are all more effective when given by injection.

MISCELLANEOUS SUBSTANCES USED FOR THEIR EFFECT ON THE ALIMENTARY TRACT

Carminatives are substances which are used to assist in expelling gas from the stomach and intestines. Their mode of action is unknown. They include peppermint, dill, anise and other herbs which are commonly included in liqueurs.

Charcoal is also used for flatulence to adsorb gas in the stomach. It may help sometimes.

Bitters are substances taken before meals to improve appetite. They have not been scientifically investigated. They include gentian, nux vomica and quinine. Preparations can be found in the B.N.F. Dilute hydrochloric acid is sometimes combined with them.

Demulcents are supposed to coat and soothe mucous membranes. They are used in sore throat, gastritis, peptic ulcer, and in cases of ingestion of corrosive or irritant poisons. They include starch, tragacanth, acacia, mucin, raw egg-white (albumen) and milk.

Digestive Enzymes

Pancreatin, in large doses, is useful in cases of pancreatic insufficiency. It is doubtful whether there is any place in therapeutics for pepsin preparations. Papain, a proteolytic enzyme from the pawpaw melon, is used to "tenderise" meat. Diastase is included in a variety of proprietary preparations with no demonstrated therapeutic effect.

Bile Salts

Bile salts are essential for the digestion and absorption of fats and fat soluble vitamins. When there is a lack of bile salts in the intestine due to obstruction of the flow or to fistula, they may be supplied by mouth. Absorption leads to higher blood levels of bile salts in cases of obstructive jaundice, but this may be less important than preventing vitamin deficiency.

Bile salts are given as either Extract of Ox Bile, B.P. (0·5 to 1 G.) or sodium tauroglycocholate (0·1 to 0·5 G.), in enteric coated capsules after meals.

Bile Acid, as dehydrocholic acid, is a cholagogue, *i.e.* it increases the secretion of a watery bile, and is used with uncertain benefit in cholangitis in the hope of preventing ascending biliary infection. It does not materially help digestion and should not be used in the presence of complete biliary obstruction.

Dehydrocholic acid is given in tablets or capsules. The dose is 0·25 to 0·5 G. after meals.

PURGATIVES

The terms purgative, cathartic, laxative, aperient and evacuant are synonymous.

Purgatives are usually classified as bulk, lubricant and irritant. Whilst some of the last group can certainly cause an enteritis the term "irritant" is not very suitable for, say, senna which acts by stimulating the motor

THE COMMONLY USED PURGATIVES

Mode of action (Site)	*Purgative*	*Dose*	*Conventional time of administration (Time to act)*
Bulk solid stool (small and large intestine)	methylcellulose	1–1·5 G.	morning (1–3 hours)
	agar	4–16 G.	
	psyllium	4–16 G.	
	bran	much	
Bulk semi-liquid stool (small and large intestine)	magnesium sulphate	5–15 G.	morning (1–3 hours)
	magnesium hydroxide	3 G.	
	sodium sulphate	5–15 G.	
	sodium potassium tartrate	5–15 G.	
Lubricant (small and large intestine)	liquid paraffin	15–45 ml.	at night or in 2–4 equally spaced doses
"Irritant" (small intestine)	castor oil	5–15 ml.	morning on an empty stomach (2–6 hours)
"Irritant" (large intestine)	phenolphthalein	0·1–0·2 G.	night (6–8 hours)
	cascara	120–150 mg.	night (8–12 hours)
	senna fruit	0·6–2·0 G.	night (6–10 hours)
	bisacodyl	5–10 mg.	night (6–10 hours)

nerve plexus of the large intestine. The time a purgative takes to act determines whether it should be given in the morning or evening and will be found in the table on p. 319, together with the dose.

Bulk Purgatives

Bulk purgatives act by increasing the volume of intestinal contents and so encouraging normal reflex bowel activity. They include two rather different groups of substances:—

Hydrophilic Colloids and Indigestible Vegetable Fibre

These promote a soft, solid stool.

Methylcellulose is soaked in water overnight and forms a colloidal solution. Tablets and granules are available. It is also used (taken as a solid) in the treatment of obesity, to provide a feeling of satiety after meals, and is sometimes useful in the control of colostomies. Sodium carboxymethylcellulose is used similarly.

Agar is obtained from seaweed. With water it swells and forms a jelly.

Psyllium Seeds contain mucilage which swells with water. Various other plant mucilages are used including slippery elm and plantago.

Bran, the residue left when flour is made from cereals, is widely used to add bulk to the diet. If a lot is eaten with a very low fluid intake it can cause intestinal obstruction.

Prunes and Figs act as bulk purges and also contain mild irritant organic substances. It should be remembered that Compound Syrup of Figs, B.P.C., and proprietary preparations in which the word "fig" is prominent, suggesting very mild and "physiological" action, owe most of their efficacy to the substantial doses of cascara or senna which are incorporated.

Bulk purgatives are often combined with liquid paraffin and irritant purges in proprietary preparations.

Inorganic Salts

Inorganic salts which are but little absorbed increase the bulk of intestinal contents by osmotic effect, retaining water in the intestinal lumen or, if given as hypertonic solution withdrawing it from the body. These promote fluid stools. The principal ions which are but little absorbed are magnesium, sulphate, phosphate and tartrate. The principal substances used as saline purges are magnesium sulphate (Epsom salt), sodium sulphate (Glauber's salt) and sodium potassium tartrate (Rochelle salt); the latter mixed with tartaric acid and sodium bicarbonate as in Compound Effervescent Powder, B.P. (Seidlitz powder) makes a not unattractive effervescent drink which is promoted also for its psychological effect when taken on getting up in the morning. All saline purges are nauseous if taken in too little water; about a cupful is minimal, except with magnesium hydroxide which is insoluble in water and is also used as a gastric antacid. The soluble magnesium salts formed in the alimentary tract act as a saline purge. It is relatively feeble and much used for children and for counteracting the constipating effects of aluminium and calcium salts in gastric antacid therapy. It is often combined with liquid paraffin in an emulsion.

In patients with renal failure the small amount of magnesium absorbed when the sulphate is frequently used can be enough to cause magnesium poisoning, the central nervous system effects of which are not dissimilar from those of uræmia. Magnesium poisoning can also occur with hypertonic enemas for lowering intracranial pressure. Again the symptoms of poisoning and those of the disease process may be confused.

Lubricant Purgatives

Liquid paraffin, a mineral oil, is the only important example of this group. It is chemically inert and is not digested. It is tasteless although some find its oiliness nauseating. It is generally said to act by lubricating the bowel, although only about the last few feet can be in need of this, for elsewhere the contents are fluid. Paraffin has been said to increase the rate of passage of small intestinal contents and it may be this effect rather than the lubricant and softening powers of the oil that promotes the passage of softer fæces. It is often given in an emulsion with magnesium oxide or phenolphthalein. It is perhaps best not taken with meals as it delays gastric emptying.

Liquid paraffin is particularly useful when straining at stool may be painful or dangerous, as after anal surgery or in cardiac disease, although it may retard healing of anal wounds. Some paraffin is absorbed from the intestine and collects in the mesenteric lymph nodes where paraffinomas may form. Absorption of fat-soluble vitamins is reduced, but there is no conclusive proof that harm has resulted from either of these effects, although harm is clearly possible.

Liquid paraffin (or other oils) taken over long periods orally, or as nasal drops, may cause chronic lipoid pneumonia, especially in the old or very young. An unusual case resulted from successful attempts by a patient to lubricate his larynx with liquid paraffin.

Continuous leakage of oil with some fæces into the rectum may tend to discourage return to the normal state in which the rectum is empty until just before defæcation. In addition large doses may leak out of the anus causing both physical and social discomfort. Liquid paraffin may not be as harmless as its chemical inertness encouraged doctors once to assume (*1*).

"Irritant" Purgatives

Castor Oil acts as a purgative after hydrolysis in the small intestine where the irritant ricinoleic acid is formed. The liquid contents of the small intestine pass rapidly onwards, resulting in a soft or fluid stool after 2 to 6 hours. Having regard to the fact that it has to be digested, castor oil should obviously be given on an empty stomach. The ricinoleic acid is absorbed and there is insignificant irritation of the large intestine. Colic (griping) is usually trivial, and so complete is the evacuation of the intestine that there is usually constipation afterwards. Castor oil is therefore chiefly used as a "once for all" purgative, as after a dietetic error. Its irritant action is powerful enough for it to be used to start pregnant women in labour.

Most patients find castor oil very objectionable to take. It is less offensive if given well cooled and floating in fruit juice, milk or whisky according to taste.

Castor oil is also used in ointments, hair lotions and eye drops as a simple non-irritant lubricant and vehicle.

Phenolphthalein. The purgative action of phenolphthalein was discovered in 1900 by Vamossy who was investigating its properties because the Hungarian government wished to use it to "denature" artificial wines. He administered it to a pet dog which seemed unmoved although it later passed a constipated stool. Unsuspecting, Vamossy and a colleague took 1·5 and 1 G. each (normal adult dose, 0·1 to 0·2 G.) and in a few hours passed 3 to 5 watery stools, repeated in the evening and again the following morning. They reported no griping and their work, unspecified, was not hindered. Clinical trials followed and phenolphthalein was introduced into clinical practice in 1902. Stories that phenolphthalein was put in wine and its purgative action discovered by the general population are denied by Vamossy (*2*).

Solid phenolphthalein is dissolved in the small intestine, a little is absorbed and excreted in the urine and bile. It stimulates the colon directly. The excretion of some in the bile tends to prolong its action, as Vamossy discovered. If the urine or faeces are alkaline they will become red and the patient may become needlessly alarmed.

Phenolphthalein is a very safe and reliable drug and is therefore widely incorporated in proprietary purgatives, including those sold in the form of chewing gum and sweets, for it is tasteless. Occasionally a rash occurs which may evade diagnosis, for it may never occur to the patient to volunteer the fact that she is using purgatives.

The Anthracene Group of Irritant Purgatives

This group includes cascara, senna, rhubarb and aloes; all vegetable in origin. In the small intestine soluble anthraquinone derivatives are liberated and absorbed. These are excreted into the colon and act there, along with those that have escaped absorption, probably after being chemically changed by bacterial action. They are said to stimulate Auerbach's plexus in the large intestine and so to provide "physiological purgation". Enough may be excreted in the milk to affect an infant.

This group of purgatives is sometimes described as the "emodin group" as emodin was thought to be the active principle. In fact it is merely one of the active substances and perhaps not even the most important.

Patients taking senna or rhubarb may notice their urine is coloured brown (if acid) and red (if alkaline) due to the presence of chrysophanic acid. Prolonged use of this group can cause melanosis of the rectum.

Erratic results with these purgatives, which are usually crude plant extracts, has in the past been due not only to the marked individual variation which occurs and to the development of tolerance but also to the absence of methods of biological assay, employment of which has now revealed great variations in potency of official preparations. Biologically standardised senna preparations are available.

Cascara is obtained from the Californian buckthorn. It is popular.

Senna is obtained from an Arabian shrub. Extracts of the fruit (pod) are said to be less griping than of the leaf, and these are used in the modern biologically standardised preparations. For those who like ritual and are not scientific about dosage, the practice of soaking pods in water and drinking the extract may be preferred.

Rhubarb (a Chinese plant) and **Aloes** are still supplied in the more old-fashioned mixtures. There is nothing much to be said either for or against them.

Other Purgatives

Bisacodyl (Dulcolax) is a synthetic substance. It is rare for a new purgative to be introduced for, with the range of drugs available, research by a commercial organisation would not offer very high prospects of financial return and academic organisations, not surprisingly, see little of interest in the study of purgatives.

Bisacodyl was introduced in 1953. It is effective orally and as a suppository and is said to stimulate the colon by direct action on the muscle. In a geriatric unit it was found that bisacodyl suppositories reduced the need for regular enemas in some patients (3). There are no reports of toxicity yet.

The **Drastic Purgatives** (jalap, colocynth and podophyllum) are obsolete as they are too drastic, and so is croton oil. Sulphur (brimstone), though not drastic, is obsolete because of offensiveness.

Mercury as calomel (mercurous chloride) or the metal finely divided with chalk (grey powder) has been used as a purgative, especially in children. However the dangers of mercury poisoning are substantial and mercury is no longer used as a purgative, or even in "teething powders" in which it was incriminated as a cause of pink disease and the nephrotic syndrome. The substitution of phenolphthalein for calomel in these damnable domestic remedies has followed a public outcry. This may result in disconcerting mauve or red colouration of babies' napkins.

CONSTIPATION

Constipation may occur with any acute illness, especially if it involves confinement to bed and is accompanied by loss of appetite. Dependence on others for assistance to the water closet or, worse, to bring a bedpan, is also a factor. The bedpan is not only objectionable as a cause of constipation, but it has also been shown that its use requires a 50% greater oxygen consumption than does use of a bedside commode, so that a bedpan should only be inflicted on those patients for whom it is absolutely necessary. These are fewer than is sometimes imagined (*4*). If severe enough to warrant attention this kind of constipation can usually be dealt with by bulk purgatives, by senna or cascara or by suppositories of glycerine or bisacodyl.

Constipation is a usual accompaniment of painful anal lesions because when defæcation hurts it is postponed for as long as possible, with the result that the motion becomes harder and so hurts even more when it is eventually passed. This vicious circle is best broken by cure of the anal lesion, but saline purgatives to make the stool semi-fluid may give relief temporarily. Constipation may be part of the syndromes associated with obstruction of the bowel, but other symptoms are always more prominent; treatment is of the cause, and purgatives are dangerous.

It is important to ensure that the patient stops taking purgatives after resumption of normal life, for a common cause of constipation is purgative "addiction". This may arise following an illness or in pregnancy, or the individual may have the mistaken notion that a daily bowel motion is essential for health, or that the bowels are only incompletely opened by nature, and so indulge in regular purgation. This effectively prevents the easy return of normal habits because the more powerful purges empty the whole colon, whereas normal defæcation empties only the descending colon. Cessation of use after a few weeks is thus inevitably followed by a few days' constipation whilst sufficient material collects to restore the normal state. This may be claimed by the patient as evidence of the continued necessity for purgatives. Patients feel they understand their own bowels far better than anyone else possibly could, an opinion they seldom extend to other organs, except perhaps the liver.

To prevent purgative "addiction" is easier than to cure it.

Purgatives are sometimes indicated before certain X-ray examinations (cascara, senna), for the removal of ingested poisons (a saline purge or castor oil), in hepatic coma (magnesium sulphate), in megacolon and with some drugs that cause constipation, such as the ganglion-blocking agents ("irritant" purgatives or enemas assisted by choline drugs).

In general, choice of a purgative is not very critical. Correction of habitual constipation is best achieved by saline bulk purges or senna. Of the "irritant" purges senna is perhaps the least objectionable.

Excessive use of "irritant" purgatives may, especially in the old, lead to severe water and electrolyte depletion, even to hypokalæmic paralysis (5).

"Irritant" purgatives are dangerous if given to patients with undiagnosed abdominal pain, inflammatory intestinal disease or obstruction. Nor should they be used to get rid of hardened masses of fæces in the rectum, for they will fail and cause pain. Digital removal is required. Purgatives should be avoided in patients taking antimicrobials orally as they may precipitate an attack of diarrhœa. Routine use of purgatives in children, on the principle that a "good clear out" is healthful, is deplorable. In pregnancy constipation is best treated by the milder purgatives (*e.g.* senna) as vigorous purgation can cause abortion. The use of vigorous purgation, traditionally with castor oil, to promote the onset of labour is unpleasant for the patient and not particularly effective.

All "irritant" purgatives can cause colic and this can be combatted, if necessary, with atropine or similar drugs.

There has been very little scientific study of purgatives in man. The importance of psychic factors in one study is indicated by the observation that after the substitution of an "inert placebo . . . an average of almost one bowel movement a day was reported by patients who claimed to be constipated. . . . At least, in our clinics, constipated persons are those who think they are not having enough bowel movements."*

In this study a beverage containing bran extract was not distinguished from a placebo by 40 normal subjects nor by 20 constipated patients. This does not, of course, condemn bran, but only bran in the form and dose used in this experiment, although it is permissible to expect similar results from bran in any form or dose.

There are innumerable preparations of purgatives, many of the proprietary ones being very elegant and pleasanter than the official preparations. Both are effective, except some of the official anthracene group, but elegance must be paid for.

Suppositories may be used to obtain a bowel action. They usually contain a mild irritant, glycerine or soap. Occasionally drugs such as aminophylline or digoxin are given by this route for their systemic effect.

* Greiner, T., Bross, I., and Gold, H. (1957). *J. chron. Dis.*, **6**, 244.

For anal and rectal disease suppositories which are astringent (hamamelis), or which provide an inert coating of the mucous membrane (bismuth subgallate) or local analgesia (lignocaine) are used as necessary.

Enemas produce a motion by distending the bowel. They have the objection of requiring time and equipment (*6*) as well as having, in some patients, psychological disadvantages. Habituation may occur. Plain water or a soapy solution are generally used.

Turpentine enema is a folk remedy used to promote the passage of gas in distended patients. Whether it does this more successfully than a simple enema is unproved. Turpentine is a very strong irritant.

Enemas to be retained may be used for a variety of conditions. To reduce intracranial pressure for a few hours 150 ml. of saturated magnesium sulphate solution is slowly run into the rectum. It acts by withdrawing water from the body into the bowel. Magnesium poisoning may occur in patients with poor renal function.

Paralytic Ileus

When this condition is due to potassium deficiency the treatment to remedy it is clear enough. In other cases there is a choice of three courses as far as drugs are concerned, to give no drugs at all, to stimulate the intestine with morphine which increases tone but not propulsive power, or to use choline drugs. No evidence exists as to which is the best course, but it is probably wisest to adopt the first or perhaps the second. Other aspects of treatment (intestinal suction and control of electrolyte balance) are beyond the scope of this book.

DIARRHŒA

Diarrhœa may be controlled by a variety of drugs which have no effect on the cause, but, as always, removal of the cause is obviously the best treatment. Symptomatic and specific treatment are often combined, as for instance in dysentery where an antimicrobial such as a sulphonamide or amœbicide, may be given together with a kaolin or chalk mixture. If a severe diarrhœa cannot be quickly controlled, replacement of the abnormal losses of water and electrolytes, including potassium, is essential.

Drugs used in the treatment of diarrhœa fall into three classes, but are often used in combination:—

Adsorbent powders, kaolin, chalk.
The opium group of drugs.
Anticholine drugs.

Adsorbent Powders. These are generally thought to act by providing a coating for the bowel and by adsorbing toxic substances, both [illegible] factory explanations. They probably do not coat the bowel; adsorption is not specific and there is no reason to believe that most of their adsorptive capacity is not taken up by non-toxic substances. But whatever the explanation they undoubtedly often work. Kaolin or chalk are commonly used in mild cases, either as powders, 2 to 4 G. 4-hourly, or more often as mixtures (Kaolin Mixture, B.P.C., or Chalk Mixture, B.P.C., 30 ml. 4-hourly). Pectin can be used like kaolin; apples contain much pectin.

The Opium Group of Drugs act directly on the smooth muscle of the bowel reducing peristalsis (p. 159). Kaolin or chalk are often reinforced by combining them with morphine (Kaolin and Morphine Mixture, B.P.C., Chalk and Opium Mixture, B.P.C.) and are invaluable symptomatic remedies in acute cases. The dose is 15 to 30 ml. not more often than 4-hourly. An alternative preparation for acute use is Chloroform and Morphine Tincture, B.P.C. (chlorodyne), 0·3 to 1 ml. Other morphine-like drugs, but not pethidine, can be used, and codeine is the best for routine use in simple chronic diarrhœa (7). Soap with Opium Pills, B.P.C., can be used, 1 to 2 pills repeated 4-hourly as necessary, but offer no advantage over the mixtures except that they are more convenient for travellers. Retention enemas containing opium or morphine are sometimes used in chronic cases.

Anticholine Drugs such as propantheline, atropine or belladonna are sometimes helpful in chronic diarrhœas where it is undesirable to use opiates indefinitely, but intestinal paralysis may be precipitated by large doses of propantheline which also blocks autonomic ganglia.

Ulcerative Colitis

Innumerable treatments have been advocated in ulcerative colitis and general management of nutrition and electrolyte balance is often all-important. Opiate drugs and occasionally propantheline are useful to reduce the frequency of bowel motions and such symptomatic remedies, plus rest, are all that is needed in many cases.

A well-designed clinical trial (8) has shown that corticotrophin (80 units of the gel i.m. daily) controls severe attacks of ulcerative colitis more effectively than cortisone (50 mg. cortisone and 1 G. potassium chloride orally 4 times a day) but only at the price of more complications and a higher relapse rate with the corticotrophin. It is therefore recommended that corticotrophin be used only in those who fail to respond to cortisone or in severe cases where the immediate benefits of more effective control outweigh the longer term risks. Maintenance treatment with cortisone is ineffective in preventing relapse. The authors of this investigation point out a disadvantage of long-term therapeutic trials nowadays, that new remedies may be introduced whilst a trial is still in progress. In this particular case prednisone, prednisolone and triamcinolone were all introduced during the trial of cortisone and corticotrophin. It may be that the newer steroids are as effective as corticotrophin. Symptomless perforation of the bowel can occur in patients taking steroids. Local treatment (slow rectal infusion of 100 mg. hydrocortisone hemisuccinate nightly) has given good results in many patients and a combination of oral prednisolone (5 mg. 4 times a day) with local hydrocortisone as above seems particularly effective.* Prednisolone-21-phosphate, equivalent to 20 mg. prednisolone, can be used by the patient as disposable plastic bag enemas.† Sulphonamides and antibiotics have been used for many years in ulcerative colitis with benefit in some cases, but recently claims have been made that dramatic improvement can be achieved with an azo compound of a sulphonamide, sulphasalazine (Salazopyrin). This drug is said to be far more effective than other sulphonamides, but properly controlled therapeutic trials are lacking so that it is impossible at present to form a just opinion of the merits of the drug in this very variable disease. Surgery is often essential in very severe cases.

GUIDE TO FURTHER READING

On Antacids and Peptic Ulcer

(Further references to the effects of anticholine drugs on the alimentary tract are given on p. 248)

(*1*) KIRSNER, J. B. (1958). Current status of therapy in peptic ulcer. *J. Amer. med. Ass.*, **166**, 1727.
(*2*) CODE, C. F. (1951). The inhibition of gastric secretion. *Pharmacol. Rev.*, **3**, 59.
(*3*) JONES, F. A., and TANNER, N. C. (1958). Peptic ulcer. *In* Modern Trends in Gastro-enterology. 2nd series. Ed. F. A. Jones. London: Butterworth.
(*4*) DOLL, R., and PYGOTT, F. (1952). Factors influencing the rate of healing of gastric ulcers, admission to hospital, phenobarbitone and ascorbic acid. *Lancet*, (*i*), 171.
(*5*) DOLL, R., FRIEDLANDER, P., and PYGOTT, F. (1956). Dietetic treatment of peptic ulcer. *Lancet*, (*i*), 5.
(*6*) DOLL, R., JONES, F. A., and PYGOTT, F. (1958). Effect of smoking on the production and maintenance of gastric and duodenal ulcers. *Lancet*, (*i*), 657.

On Purgatives, Constipation and Diarrhœa

(*1*) MORGAN, J. W. (1941). The harmful effects of mineral oil (liquid petrolatum) purgatives. *J. Amer. med. Ass.*, **117**, 1335.
(*2*) VAMOSSY, Z. VON (1936–7). Is phenolphthalein harmful? *Amer. J. dig. Dis.*, **3**, 22.
(*3*) CLARK, A. G. N. (1957). A new evacuant suppository. *Brit. med. J.*, (*ii*), 866.

---

* TRUELOVE, S. C. (1960). *Brit. med. J.*, (*i*), 464.
† MATTS, S. G. F. (1960). *Lancet*, (*i*), 517.

(4) Benton, J. G., Brown, H., and Rusk, H. A. (1950). Energy expended by patients on the bedpan and bedside commode. *J. Amer. med. Ass.*, **144**, 1442.
(5) Annotation (1959). A hazard of purgation. *Brit. med. J.*, (*i*), 38.
(6) Brockbank, W. (1954). Ancient Therapeutic Arts. London: Heinemann.
(7) Connell, A. M., and Kellock, T. D. (1959). Treatment of chronic non-specific diarrhœa, a clinical comparison. *Brit. med. J.*, (*i*), 151.
(8) Truelove, S. C., and Witts, L. J. (1959). Cortisone and corticotrophin in ulcerative colitis. *Brit. med. J.*, (*i*), 387.

Chapter 19

HISTAMINE AND ANTIHISTAMINICS

HISTAMINE

HISTAMINE is a naturally occurring amine of great interest to pharmacologists but with only a modest importance for physicians. It occurs naturally in an inactive bound form in most body tissues and pharmacologically active free histamine is released in response to injury, such as physical trauma of any kind or antigen-antibody reactions. There are also various chemicals which have power to release histamine. The more powerful of these (proteolytic enzymes and snake venoms) have no place in therapeutics, but a number of useful drugs, such as tubocurarine, morphine and even some antihistaminics, also release histamine, although not usually enough to be dangerous. The physiological role of histamine is still not known; one possible function is in the gastric mucosa, where the hormone gastrin may increase secretion by inducing histamine release. The actions of histamine which are clinically important are those on:—

Gastric Secretion. Histamine increases the acid and perhaps the pepsin content of gastric juice. This effect is antagonised only trivially by atropine and not at all by antihistaminics. To test the ability of the stomach to secrete acid 100 mg. of the antihistaminic mepyramine is first given i.m. to reduce the effects of histamine elsewhere in the body. Twenty minutes later 0·04 mg. Kg. of histamine acid phosphate is given s.c. (2·75 mg. of the acid phosphate are equivalent to 1 mg. of histamine base), and the stomach contents sampled continuously by tube (*1, 2*). This "maximum" histamine test supplants the older test in which 0·5 to 1 mg. of histamine acid phosphate was used without an antihistaminic, because the former is reasonably quantitative, which the older test is not. The "maximum" histamine test gives a measure of the total acid-secreting cell volume of the stomach* and may prove useful as a guide to therapy, especially with regard to how radical a surgical operation for the treatment of peptic ulcer need be. The test has also caused a revision of the definition of achlorhydria, which is a rarer condition than was previously supposed. In 500 consecutive tests it was found that the only patients who failed to lower the acidity of their gastric juice below pH 6 were those with pernicious anæmia, and a definition of achlorhydria has been proposed as failure to lower the gastric pH below 6 in response to maximal histamine stimulation (*1*).

---

* CARD, W. I., and MARKS, I. N. (1960). *Clin. Sci.*, **19**, 147.

The tubeless method of measuring gastric secretion has not, unfortunately, allowed the stomach tube to be discarded. Cation-exchange resin is used, from which hydrogen ions displace the dye Azure A (Diagnex). The dye is then absorbed from the small intestine and excreted in the urine where its concentration is measured. False negative results arise from defective absorption of Azure A in pyloric obstruction, malabsorption syndromes or severe diarrhœa, and false positive results occur because the cation can be displaced not only by hydrogen ions but also by magnesium, iron, aluminium (including kaolin) or calcium, so these substances should be eschewed for two days before the test. Nevertheless the tubeless method has a place for the rapid screening of patients although it is unsuitable for quantative studies.

Smooth Muscle. In general histamine stimulates smooth muscle (excepting arterioles, but including the larger arteries) throughout the body. Stimulation of the pregnant human uterus is insignificant. A brisk attack of bronchospasm may be induced in subjects who have any allergy, particularly asthma.

Arterioles. These are dilated, with a consequent fall in blood pressure. The characteristic throbbing headache that occurs after histamine injections is due to stretching of pain sensitive structures in the dura mater by the alterations in pressure in blood vessels and cerebrospinal fluid (*3*).

Capillaries. These dilate and their permeability to plasma is increased, which responses comprise two parts (the local red response and the wheal) of the "triple response" described by Sir Thomas Lewis (*4*). The third part is arteriolar dilatation due to an axon reflex.

Suprarenal Medulla. This is stimulated to release adrenaline and noradrenaline in amounts which are insignificant in normal subjects but which are sufficient to raise the blood pressure in patients with phæochromocytoma in whom i.v. injection of histamine is sometimes used as a diagnostic test (p. 282).

General

Histamine is insignificantly absorbed from the alimentary tract and is largely metabolised in the body, although a little appears in the urine. After s.c. injection its effects persist for about half an hour. True tolerance to histamine does not occur to any significant extent and there is no good evidence that courses of histamine injections to "desensitise" allergic subjects are of any value.

The only important clinical use of histamine is in gastric function tests. Attempts to utilise its vasodilator action in Ménière's syndrome and peripheral vascular disease have been given up. It has been used in migraine with dubious benefit; the psychological reaction to a substantial injection may be profound.

Toxic effects of histamine are an extension of the actions described above,* with, in addition, stimulation of the smooth muscle of the intestine which is not seen at ordinary doses. The main features are circulatory collapse and bronchoconstriction. The most rapidly effective antidote is adrenaline, and antihistaminics may be given as well, by injection in severe cases.

ANTIHISTAMINICS

When it became clear that release of histamine by tissue injury had harmful effects it was evident that histamine antagonists might have therapeutic importance, especially in allergic conditions.

The effects of histamine can be opposed in four principal ways:—

1. By using a drug with opposite effects, *e.g.* histamine constricts and adrenaline dilates the bronchi.

2. By preventing histamine from reaching its site of action, *e.g.* by competition, the antihistaminics.

3. By accelerating the destruction of histamine in the body. Attempts have been made to use the enzyme histaminase (di-amine oxidase) for this purpose, but it has not proved useful.

4. By preventing the release of histamine, adrenocortical steroids can suppress the effects on the tissues of antigen-antibody reactions.

The term antihistaminic is confined to drugs which act by competition (group 2 above) although the formulæ of some differ completely from that of histamine. Substances capable of this effect were discovered in 1937, and by 1947 the antihistaminics diphenhydramine and pyribenzamine were in clinical use. Since their introduction the number of antihistaminics available has increased rapidly. This is both because they are relatively easy to make, and because they control some allergic conditions without curing them, so that they are in constant demand. A substantial proportion of the population, it is said as much as 10 to 15%, suffer allergic reactions at some time in their life, so that an effective antihistaminic can be very profitable commercially even though only a minority of sufferers are benefitted by the drugs.

The term antihistaminic is not a very satisfactory one, for not only do the drugs fail to prevent histamine-induced gastric secretion but they have numerous other actions and are used as hypnotics, antiparkinsonian remedies, antitussives and in motion sickness, actions which are not related to antihistamine power. Although the drugs differ in various ways these are not of very great importance, except to an occasional individual patient, and so they can be conveniently discussed together. The ideal antihistaminic, *i.e.* a drug which has no additional actions, has yet to be found.

---

* *I.e.* strictly they are side-effects.

Actions of Antihistaminics

Antihistaminics oppose all the effects of injected histamine except that on gastric secretion. They also affect the central nervous system, usually to depress but sometimes to stimulate. They can occasionally make petit mal worse. They can be beneficial in Parkinsonism and motion sickness and this may be attributable to their anticholine or atropine-like actions. Some also have weak quinidine-like and either anti-adrenaline or adrenaline-potentiating effects. They are local anæsthetics.

Antihistaminics are readily absorbed from the alimentary tract and are usually administered orally three or four times a day. They can also be given i.m. or i.v. They are mostly metabolised in the liver, but excretion of enough in the milk to affect infants has been recorded.

Unwanted effects are common with antihistaminics and can be very troublesome although persistence is worthwhile if a good therapeutic effect has been obtained, as tolerance to the side-effects sometimes develops. Some of the commonest effects are sedation, dizziness, fatigue, insomnia, nervousness, tremors, gastro-intestinal disturbance and dry mouth. Dermatitis and agranulocytosis can occur. Severe poisoning due to overdose results in coma and sometimes in convulsions. If analeptics are needed they should be given cautiously because of the risk of causing convulsions. The administration of barbiturates for convulsions can lead to respiratory failure, but may be necessary. Hyperpyrexia can occur.

Uses of Antihistaminics

Antihistaminics in Allergic Conditions

Histamine is released in many allergic states, but it is not the sole cause of symptoms. In urticaria histamine released in the epithelium has to diffuse to the blood vessels before producing its effects (extrinsic histamine effect) but in asthma the histamine is released in the bronchial muscle cells, *i.e.* at the site of action (intrinsic histamine effect). This may explain why antihistaminics are effective therapy in urticaria but not in asthma, but is probably a gross oversimplification.

Failure to respond is also due to the fact that active substances other than histamine are released in allergic states. In severe allergies adrenocortical steroids are useful.

Urticaria (named after its similarity to the sting of a nettle, Urtica), and angioneurotic œdema usually respond well to antihistaminics although severe cases are relieved more quickly by adrenaline (0·1–0·2 ml. adrenaline, 1 : 1,000, s.c.). Serum sickness only responds partially.

Hay fever and allergic rhinitis often respond well, but nasal sprays containing vasoconstrictor drugs (phenylephrine, ephedrine, naphazoline) may give more relief. Any relief obtained from antihistaminics in the common cold is due to a reduction of secretions and perhaps to control of any slight allergic element there may be in the response to infection. Reports that antihistaminics aborted the common cold resulted from these effects, from failure to exclude patients with allergic rhinitis and to the therapeutic effect of suggestion. They provide a salutary lesson on observer bias, placebo-reactors, failure to appreciate that accurate diagnosis is an essential prelude to therapeutic experiment and faulty presentation of results (*5*, *6*).

Asthma responds poorly or not at all to antihistaminics although the atropine-like effect on the bronchi may be useful. However, if tried, they should be stopped as soon as it is clear that they have provided no benefit because it is known that they can increase bronchoconstriction, perhaps even by causing histamine release themselves (*7*).

Allergies of the skin sometimes respond to antihistaminics, although the drugs can themselves cause rashes. It is sometimes possible to control a drug rash whilst persisting with the causative drug on the rare occasions when such persistence is essential.

Relief of itching is probably chiefly due to the sedative, or if applied locally, to the local analgesic effect. Prolonged local application is undesirable as the drugs are liable to cause sensitivity reactions. Antihistaminics may be used prophylactically against serum or drug allergies on the rare occasions when these can be anticipated. They do not invariably give protection. They are useless against hæmolytic and pyrogenic reactions to blood transfusion.

They may be used systemically or locally against bee or wasp stings, which both contain histamine and cause histamine release in the tissues, but are only worth giving to people who are known to react excessively to the stings. Administration needs to be very prompt to be useful.

Other Uses of Antihistaminics

Antihistaminics are used in Parkinsonism (diphenhydramine), and also as hypnotics (promethazine). A number of anti-emetics happen also to be antihistaminics (p. 219).

Preparations of Antihistaminics

The doses of the main antihistaminics are given in the table on p. 335, which includes more than any one physician will require. There are yet others, but little useful purpose would be served by listing them. They are all about equally useful or useless, as the case may be.

THE PRINCIPAL ANTIHISTAMINICS

Name	*Oral dose (i.m. or i.v. dose in brackets)*	*Remarks*
mepyramine maleate (Anthisan)	25–50 mg. 3 or 4 times a day	A satisfactory drug as antihistamines go.
diphenhydramine hydrochloride (Benadryl)	25–50 mg. 4 times a day (10–50 mg. i.m./i.v.)	Sedation and atropine-like effects marked. Also used in Parkinsonism and motion sickness.
promethazine hydrochloride (Phenergan)	25–75 mg. at night or twice a day (20-50 mg. i.m. i.v.)	A good general purpose drug. Acts for 20 hrs. Sedation marked. Avomine is the chlorotheophyllinate, is especially used in motion sickness but is probably not superior to promethazine itself.
phenindamine tartrate (Thephorin)	25–50 mg. 4 times a day	A good general purpose drug. More likely to cause cerebral stimulation than sedation. May be used in morning, after, say, promethazine at night.
tripelennamine hydrochloride (Pyribenzamine)	50–100 mg. 3 times a day	Causes sedation.
chlorcyclizine hydrochloride (Histantin)	25–50 mg. 2 or 3 times a day	Causes sedation.
dimenhydrinate (Dramamine)	25–50 mg. up to 6 times a day (25–100 mg. i.m./i.v.)	Injection i.v. must be very slow. Chlorotheophyllinate of diphenhydramine. Sedation marked. Used in motion sickness, probably not superior to diphenhydramine.
chlorpheniramine maleate (Piriton)	2–4 mg. 3 or 4 times a day (10–20 mg. i.m./i.v.)	An alternative.

GUIDE TO FURTHER READING ON HISTAMINE AND ANTIHISTAMINICS

(*1*) CARD, W. I., and SIRCUS, W. (1958). *In* Modern Trends in Gastroenterology. 2nd series. Ed. F. A. Jones. London: Butterworth.

(*2*) KAY, A. W. (1953). Effect of large doses of histamine on gastric secretion of HCl. An augmented histamine test. *Brit. med. J.*, (*ii*), 77.

(*3*) PICKERING, G. W. (1933). Observations on the mechanism of headache produced by histamine. *Clin. Sci.*, **1**, 77.

(4) Lewis, T., and Grant, R. T. (1924). Vascular reactions of the skin to injury. *Heart*, **11**, 209.
(5) Editorial (1950). Antihistaminic drugs and the common cold. *Brit. med. J.*, (*ii*), 448.
(6) Report on antihistaminic agents in the prophylaxis and treatment of the common cold. *J. Amer. med. Ass.*, 1950, **142**, 566.
(7) Annotation (1955). Antihistamines and asthma. *Lancet*, (*ii*), 1182.
(8) Wolstenholme, G. E. W., and O'Connor, C. M. (1956), editors. Histamine. London: Churchill.

Chapter 20

VITAMIN K AND ANTICOAGULANTS

Anticoagulants act on various components of the blood clotting mechanism, a brief account of which follows:—

1. Damaged PLATELETS + Antihæmophilic globulin + Christmas factor + Factor V + Factor VII + Ca″ → THROMBOPLASTIN
and at the same time,
Damaged TISSUES + Factor V + FACTOR VII → THROMBOPLASTIN
2. Then, THROMBOPLASTIN + Ca″ + PROTHROMBIN → THROMBIN
Thrombin liberates more thromboplastin from the platelets and hence catalyses its own production.
3. Then, THROMBIN + FIBRINOGEN → FIBRIN.

Thromboplastin is a protein present in most cells and in platelets, its formation is depressed by lack of either antihæmophilic globulin or Christmas factor.

Antihæmophilic Globulin and Christmas factor, see p. 338.

Factor V is a component required for thromboplastin formation, which may become deficient in liver disease, some acute infections and occasionally in secondary carcinoma.

Factor VII is also required for thromboplastin formation; it is produced in the liver, and formation is reduced in vitamin K deficiency, liver disease and by the coumarin group of drugs.

Calcium Ions. Plasma calcium levels never fall low enough *in vivo* to depress clotting. Citrate and oxalate prevent clotting by converting the calcium present to an unionised and therefore inactive form. Oxalate is too toxic for use in blood intended for transfusion, but sodium citrate (50 ml. of a 4% solution to each pint of blood) is used routinely for this purpose. Massive transfusions may lead to citrate intoxication with cardiac depression and perhaps with tetany, both due to depression of ionised calcium. Calcium gluconate (10 ml. of 10% solution) should be given i.v. for this.

Prothrombin is a globulin formed in the liver, whose production is reduced in liver disease and vitamin K deficiency. Its formation is depressed by some of the coumarin group of anticoagulants.

Thrombin is a proteolytic enzyme formed from prothrombin. It is antagonised by heparin. Fibrin absorbs thrombin and hence limits extension of the clotting process.

Fibrinogen is one of the plasma proteins, reduced only in a rare congenital disorder and in certain obstetric conditions, in particular after premature separation of the placenta with liberation of thromboplastin into the circulation in repeated small amounts.

Fibrin is the protein formed from fibrinogen by the action of the enzyme thrombin. It is used as a local hæmostatic.

Platelet Deficiency is a common cause of a bleeding tendency and purpura. Drugs notorious for platelet destruction include apronal (Sedormid), arsenicals, bismuth, phenylbutazone, gold, sulphonamides, quinine and quinidine. Drugs are also frequently responsible for pancytopenia or agranulocytosis in which platelet deficiency makes a variable, but often important, clinical contribution.

Transfusion of fresh blood which has been collected with special precautions (siliconed apparatus and polythene containers) to prevent platelet destruction may help in platelet deficiency, but transfused platelets do not survive long.

Hæmophilia

Hæmophilia is characterised by deficiency of antihæmophilic globulin, which results in prolonged bleeding from even trivial wounds. Christmas disease, in which antihæmophilic globulin is normal but the Christmas factor deficient, is clinically indistinguishable from hæmophilia proper except that it occurs in women as well as in men. It is very important to recognise that local measures for the arrest of bleeding must be such as do not interfere with healing, for until healing has occurred the risk of severe hæmorrhage persists. Bleeding in these conditions can sometimes be stopped by pressure: edges of superficial wounds should be strapped, not stitched. Local applications, never injections, of thrombin or Russell's viper venom, together with fibrin or gelatin are worth trying. Fresh blood or plasma transfusion in substantial amount restores the bleeding time even to normal for a few hours. In Christmas disease stored blood is effective and frequently only small amounts are required. Antihæmophilic globulin preparations have been made, but use is still limited by supply.

Local Hæmostatics

Many preparations are available, most act by providing a network of fibres which promote coagulation. They are particularly effective on oozing surfaces, *e.g.* in tooth sockets.

Human or Bovine Thrombin is prepared as a powder; if a solution is required it must be freshly made up; homologous serum hepatitis has been transmitted by human thrombin. Thrombin is useful in hæmophilia and is used together with fibrin in neurosurgery and also when fixing skin grafts. It must never be injected.

Russell's Viper Venom (Stypven) acts as a very strong thromboplastin. It can be useful in hæmophilia and must never be injected.

Fibrin Foam is available as a dry mass of fibrils; it is usually used together with thrombin. It is absorbed in the body.

Gelatin Sponge, foam or film, is similar to fibrin, and is also absorbable.

Oxidised Cellulose (Oxycel) is not well absorbed; it is not used with thrombin on account of its acidity. It is suitable for surface hæmostasis, but should not be left on as a dressing as it interferes with repair of the epithelium.

Adrenaline may be useful in epistaxis, arresting hæmorrhage by inducing local vasoconstriction when applied by packing the nostril with ribbon gauze soaked in Adrenaline Solution, B.P.

Vitamin K

Vitamin K is a fat-soluble vitamin necessary for the formation of prothrombin and factor VII in the liver. It was discovered during feeding experiments on chicks in which it was found that deficiency of an ether-soluble substance caused a bleeding disease. At about the same time the bleeding tendency in obstructive jaundice was shown to be due to prothrombin deficiency and it was soon shown that vitamin K was effective treatment. There are two naturally occurring vitamin K's. K_1 is widely distributed in plants and K_2 is synthesised in the alimentary tract by bacteria. Bile is required for vitamin K absorption; metabolism and utilisation take place in the liver, and therefore vitamin K is not effective against hypoprothrombinæmia when it is due to severe liver damage. The response to vitamin K has been used as a liver function test in patients with prothrombin deficiency. If the blood prothrombin does not rise after administration then there is considerable liver damage. A bleeding tendency due to dietary vitamin K deficiency probably does not occur in man. However, deficiency may be due to:—

1. Abnormal alimentary tract flora, *e.g.* in newborn infants and, rarely, after antimicrobials (sulphonamides, tetracyclines).

2. Bile failing to enter the intestine, *e.g.* obstructive jaundice, biliary fistulæ.

3. Certain malabsorption syndromes, *e.g.* sprue; after extensive intestinal resections.

Vitamin K is a specific antagonist of the coumarin group of anticoagulants.

Vitamin K_1 (Phytonadione), the naturally occurring fat-soluble vitamin is the most rapidly effective vitamin K preparation, taking only 3 to 5 hours to act. An emulsion is given by slow i.v. injection, i.m. or orally. If given orally in obstructive jaundice 2 G. of bile salts should be given as well, or it will not be absorbed. The dose is 1 to 50 mg. repeated in 8 hours if necessary. Small doses (1 to 5 mg.) given repeatedly, 8 to 12-hourly, with simultaneous measurement of prothrombin times, are ideal in less urgent cases, especially if anticoagulant therapy is to be continued. They avoid the risk of over-swing with thrombo-embolism which may occur if large doses (10 to 50 mg.) are used. Vitamin K_1 should be reserved for emergencies, the cheaper analogues being satisfactory unless a rapid effect is required.

The Synthetic Vitamin K Analogues

These are suitable for use on most occasions when a vitamin K effect is required, their main disadvantage is the longer time taken to act.

Acetomenaphthone is fat-soluble, so it is not absorbed from the intestine in the absence of bile. It may be given orally but not parenterally. The dose is 5 to 20 mg. daily; it is effective in 24 hours.

Menaphthone, 1 to 5 mg. i.m. daily is an alternative.

Water-soluble Vitamin K Analogues (*e.g.* Synkavit) can be given orally, s.c., i.m. or i.v. The dose is 5 to 10 mg. daily and is effective within 24 hours. An alternative is menaphthone sodium bisulphite.

There are numerous other preparations of vitamin K analogues.

Indications for Vitamin K or its Analogues

These are :—

1. Bleeding due to the coumarin anticoagulants.
2. Hæmorrhagic disease of the newborn and prematurity.
3. Hypoprothrombinæmia in jaundiced patients, particularly before and after operation. The hypoprothrombinæmia of hepatic cirrhosis is seldom significantly improved.
4. The intestinal malabsorption syndromes, if hypoprothrombinæmia occurs.
5. Salicylate poisoning (p. 171).
6. Hypoprothrombinæmia due to antimicrobials.

Hæmorrhagic Disease of the New-born

The prothrombin level of new-born infants is low, and this is thought to be due to lack of the intestinal bacteria which synthesise vitamin K. This hypoprothrombinæmia can be corrected either by prophylactic administration of a vitamin K analogue to the mother, or by 0·5 to 1 mg. of Synkavit to the baby. Routine administration of vitamin K certainly raises the prothrombin levels but is probably unnecessary. Vitamin K_1 or an analogue should be given to premature or feeble infants and those who are bleeding or have suffered birth trauma.

Toxic Effects of Vitamin K

The natural vitamin K is not toxic in any dose, but very large amounts of the analogues may cause respiratory depression and death. In neonates 50 mg. of Synkavit has been shown to increase jaundice and hence the incidence of kernicterus, and to be no more effective than 1 mg. Some, however, prefer menaphthone sodium bisulphite as potentially less toxic.

ANTICOAGULANTS

Anticoagulants fall into two groups:—

Heparin Group. These are very rapidly effective, only act for a few hours, must be given parenterally, and are antagonised by protamine. They are effective *in vitro* as well as *in vivo*.

Coumarin Group. These take 16 to 72 hours to become effective, act for several days, are given orally and can be antagonised, though comparatively slowly, by vitamin K. They are only effective *in vivo*.

The anticoagulants are compared in the table on p. 344.

Heparin

Heparin was discovered by a medical student who was investigating the clot-promoting activity of certain phosphatides. He was surprised to find that a preparation from liver prolonged the clotting time. This was investigated and heparin was eventually isolated. It is a mucopolysaccharide found in mast cells and prepared commercially from ox lung; it is standardised on animal blood. The sodium salt dissolved in saline is used therapeutically.

Mode of Action of Heparin

Heparin is the strongest organic acid synthesised in the body and in solution carries a very strong electronegative charge which is thought to interfere with the enzymes needed for clotting. In the presence of a plasma co-factor it is mainly active as an antithrombin, but it has been pointed out that the anticoagulant property of heparin is displayed on fresh whole blood rather than on any one particular part of the clotting system (*2*). Heparin reduces the lipæmia following a fatty meal by facilitating transfer to the fat depôts. It has been suggested, but is unproved, that this action of heparin might influence atheroma and search is being made for heparin-like substances suitable for clinical trial. The antilipæmic action of heparin is quite distinct from its anticoagulant effect. Some believe that heparin is beneficial in arterial embolus not only on account of its anticoagulant properties, but also by virtue of its slight vasodilator effect which may promote collateral circulation.

Although heparin has been found in the blood of dogs after anaphylactic shock and is released from mast cells by histamine liberators, there is no evidence that it is responsible for any of the bleeding diseases.

Dose of Heparin

Heparin is ineffective by mouth. It is best given i.v. in a dose of 100 to 150 mg. (100 mg. = 10,000 I.U.). The maximum effect is immediate and rapidly wears off, little remaining after 6 hours; it is partly excreted in the urine and partly destroyed in the liver. The injections should therefore be repeated at least 6-hourly; 4-hourly is the counsel of perfection. Injections are often given at 8-hourly intervals or longer, but it should be realised that this only provides intermittent effect. Injections i.m. and s.c. with and without hyaluronidase, and various depot preparations can be used and give satisfactory delayed coagulation, but they are liable to cause painful hæmatomas. If long-term therapy is intended one of the coumarin group of drugs is started orally at the same time as the heparin.

Control of Heparin Therapy. The clotting time should be kept above 15 minutes (normal 5 to 7 minutes). The clotting time is the time required for blood to clot in glass and is easily measured at the bedside using capillary tubes. It should be measured before heparin therapy is started and at least once daily immediately before an injection is due.

Side-effects of Heparin

Bleeding is the only serious complication of heparin therapy. It is not common, except after surgery. Transient alopecia and diarrhœa occur rarely: they are possibly due to interference with sulphonated mucopolysaccharide metabolism in the hair follicle and mucosa of the alimentary tract.

Heparin Antagonists

Protamine, a protein obtained from fish sperm, may be used to antagonise the anticoagulant action of heparin. It is as strongly basic as heparin is acidic, which probably explains its specific antagonism to the heparin group of drugs. It is given by slow i.v. injection as protamine sulphate and neutralises an equal weight of heparin. Heparin effects wear off so rapidly that protamine is rarely required. A synthetic substance hexadimethrine (Polybrene) can be used instead of protamine.

Heparin Analogues

A number of synthetic polysaccharides are being investigated in the hope of replacing heparin with a cheaper and more convenient compound, but none is yet firmly established. They include dextran sulphate and pectin sulphate.

Coumarin Group of Anticoagulants

This includes dicoumarol, ethyl biscoumacetate (Tromexan), phenindione (Dindevan), warfarin sodium, phenylpropylhydroxycoumarin (Marcoumar) and diphenadione. Dicoumarol was identified in 1941 and soon became widely used in medicine. Its onset of action is slow but its effects are prolonged. The related compound ethyl biscoumacetate is more rapidly effective but wears off quickly. Phenindione and warfarin sodium differ slightly and are generally satisfactory. The properties of these compounds are compared in the table on p. 344. Their great advantage over heparin is that they can be given orally: their chief disadvantage is the time lag before they exert their effect.

History of the Coumarin Anticoagulants

In the early 1920's a new and mysterious cattle disease began to trouble farmers in North America. It was characterised by a severe bleeding tendency and never occurred unless sweet clover, a recently introduced and useful fodder crop, had been fed to the animals. Hæmorrhage in the cattle was sometimes spontaneous, but more often followed trauma, and was serious; for example 21 out of 22 cows died after dehorning; 12 out of 25 young bulls died after castration. All had bled to death. Schofield, a veterinary pathologist who first described the disease, quotes a farmer who, "following the traditions of his elders, cut a slice of skin and cartilage from the ears of all his yearling cattle and then retired for the night. This was to have had the mysterious effect of a blood tonic. The application of ligatures the following morning saved his cattle from immediate death, but due to a continuation of the feed they all succumbed" to hæmorrhage within a few weeks.*

He observed that it was only mouldy sweet clover that was toxic and performed a simple experiment:—

"Good clover stalks and damaged clover stalks were picked from the same hay mow. The good were fed to one rabbit and the damaged to another. The rabbit which ate the good remained well, while the rabbit which ate the bad died, showing typical (hæmorrhagic) lesions. This experiment was duplicated, using a different sample of clover hay. The results were the same."

This report, and the economic importance of the disease, led to a great deal of research, which after 20 years culminated in the isolation of the toxic agent, dicoumarol.

Coumarins are present in many plants and are of great importance in the perfume industry. The smell of new mown hay and grass is due to a coumarin.

---

* SCHOFIELD, F. W. (1924). *J. Amer. vet. med. Ass.*, **64**, 553.

Mode of Action of the Coumarin Anticoagulants

These compounds all specifically prevent the formation of clotting factors, mainly factor VII and prothrombin, from vitamin K in the liver.

Dosage of the Coumarin Anticoagulants

Dosage of the most commonly used drugs is compared in the table.

A loading dose is given and this is followed by a maintenance dose, which is eventually adjusted according to the results of prothrombin estimations.

THE ANTICOAGULANTS COMPARED

	heparin	*dicoumarol*	*phenindione*	*ethyl biscoum-acetate*	*warfarin sodium*
Mode of action	principally anti-thrombin	depresses factor VII and pro-thrombin	depresses factor VII and pro-thrombin	depresses factor VII only	depresses factor VII principally
Route of administration	i.v. (or i.m.)	oral	oral	oral	oral, i.v. or i.m.
Initial dose	100–150 mg.	600 mg.	450 mg.	1,500 mg.	75–100 mg. (60–75 mg. parenteral)
Approx. maintenance dose	5–15 mg. 6-hourly	25–100 mg. daily	10–100 mg. 12-hourly	50–300 mg. 8-hourly	12·5 mg. daily
Onset of effect of single large dose	immediate	24 hrs.	12–16 hrs.	12–16 hrs.	12–16 hrs.
Peak of single large dose	immediate	40–72 hrs.	40 hrs.	24 hrs.	32 hrs.
Duration of effect	4–6 hrs.	48–120 hrs.	24–72 hrs.	24–72 hrs.	48–120 hrs.
Antagonist	protamine	vitamin K_1	vitamin K_1	vitamin K_1	vitamin K_1

Some of the initial doses recommended in this table are higher than has been considered necessary in the past, but they give rapid control without the wide swings in prothrombin level which are often seen with the slower induction periods that occur with smaller doses (7). Warfarin sodium is the only member of the coumarin group that can be given parenterally.

In general all patients whose prothrombin level is not within the therapeutic range at 16 hours require a maintenance dose on the second day of therapy, otherwise it may be delayed until the third day. The prothrombin level 40 hours after the loading dose is very important, as it generally coincides with the peak effect. The next dose will be large or small according to the prothrombin level.

If it is desired to obtain anticoagulant effect immediately it will be necessary to use heparin as well and to continue it until the prothrombin time is longer than 25 seconds, which is usually in about 24 to 40 hours.

There is greater individual variation in the duration of action of these drugs than there is in the time of onset of action, suggesting that rates of metabolism and excretion are the most important factors in determining dosage. Efficient laboratory control is vital. The clotting time, by methods practicable at the bedside, is unreliable for this purpose and Quick's one-stage "prothrombin time" is commonly used. It depends on the addition to citrated plasma of an excess of tissue thromboplastin and calcium ions and measurement of the time taken for it to clot. This procedure does not differentiate between a deficiency of factor VII or of prothrombin but it is adequate for control of anticoagulant therapy. Results can be expressed in a confusing variety of ways, of which "Prothrombin Time" and "Prothrombin Concentration" are widely used:—

The "Prothrombin Time" (normally 13 to 17 seconds) is the actual time taken for clotting under controlled conditions. This must be compared with a normal control on each estimation.

The "Prothrombin Concentration", expressed as a percentage, can be obtained by comparing the unknown plasma with serial dilutions of normal plasma.

Satisfactory anticoagulant effect is got with a prothrombin time between 25 and 40 seconds (alternatively prothrombin concentration 10 to 20% of normal). The risk of bleeding is serious if these limits are exceeded. Blood for prothrombin estimations should not be collected within 2 hours of heparin administration, and this estimation is not likely to be helpful until 16 hours after starting coumarin therapy.

Toxic Effect of Coumarin Anticoagulants

Bleeding is the only common toxic effect encountered and may occur at any site, but especially in the renal and alimentary tracts. Patients with liver disease or vitamin K deficiency are exceptionally sensitive to these compounds. Agranulocytosis has occurred rarely during phenindione therapy. Sudden cessation of long-term anticoagulant therapy may be followed by an increased liability to thrombosis. Dosage should be reduced slowly over several weeks. With phenindione the urine may turn red innocuously.

Antagonists of Coumarin Anticoagulants

Vitamin K_1 orally or i.v. will reduce the prothrombin time to normal in 3 to 5 hours. The dose given is up to 10 mg. if anticoagulant therapy is to be resumed, but may be up to 50 mg. if not (p. 339). If larger doses are used anticoagulant effect with a coumarin drug (though not, of course, with heparin) will be impossible for up to a fortnight. In the absence of bleeding an excessively long prothrombin time does not of itself demand treatment other than temporarily stopping the drug. Vitamin K analogues can be used if K_1 is not available, but they take longer to act.

Choice of Anticoagulant Drug

For brief and immediate effect there is no satisfactory substitute for heparin, i.v. or i.m.

For more prolonged treatment (weeks) the shorter-acting members of the coumarin group (*e.g.* phenindione) are the easiest to use if the patient is in hospital or otherwise under close supervision.

For very prolonged treatment (months, years), where the patient may only be seen every few weeks, the longer-acting dicoumarol is probably preferable, especially if the patient is liable to forget an occasional dose.

Indications for Anticoagulant Treatment

Myocardial Infarction. All "bad-risk" patients (*9*) should be treated with anticoagulants, that is patients with any of the following:—

1. previous myocardial infarction;
2. intractable pain;
3. extreme degree or persistence of shock;
4. significant enlargement of the heart;
5. gallop rhythm;
6. congestive heart failure;
7. cardiac arrhythmias;
8. diabetes;
9. marked obesity;
10. previous thrombo-embolic episodes or predisposing condition such as varicose veins.

In "good-risk" patients, *i.e.* those without any of the above list, the mortality rate is uninfluenced but the rate of thrombo-embolic complications is reduced. The figures proving this reduction in complications have been criticised on the ground that diagnosis of thrombo-embolism is often an indirect and subjective process, errors in which are often revealed at autopsy, and so is liable to be affected by unconscious bias.

Whether or no this criticism is considered valid it is still impossible to dogmatise on whether "good risk" cases should be treated with anticoagulants; probably they need not be so treated and exposed to the inevitable accompanying inconvenience and even danger.

But there is substantial disagreement on this point ranging from the opinion that serious thrombo-embolic complications occur often enough in mild cases to warrant treating them all (*8*), to the opinion that anticoagulants are neither necessary nor desirable in mild or "good-risk" cases (9).

The duration of anticoagulant treatment in myocardial infarction should certainly be at least 6 weeks, but some advocate 6 months, especially in male patients under 55 years of age. Women may not be benefitted by prolonged anticoagulant therapy (5).

Results of anticoagulant therapy in one large series are shown in the table.

THE RESULTS OF ANTICOAGULANT THERAPY IN A SERIES OF PATIENTS WITH MYOCARDIAL INFARCTION *

	Controls (no anticoagulants used) 442 *patients*	*Treated (with anticoagulants)* 589 *patients*
Thrombo-embolic complications	26%	11%
Deaths in first 6 weeks, excluding first 24 hrs.	23·4%	16%
Deaths preceded by thrombo-embolic episode	42% of deaths	23% of deaths
Deaths amongst patients mildly or moderately ill	14%	7%
Deaths amongst "good-risk" patients (see text for criteria)	less than 2%	less than 2%
Thrombo-embolic complications amongst "good-risk patients"	29%	9%
Episodes of hæmorrhage, *e.g.* hæmoptysis, hæmaturia, etc.	5%	13%
Deaths due to hæmorrhage	0	0

* Data from WRIGHT, I. S., *et al.* (1954). Myocardial infarction and its treatment with anticoagulants. *Lancet*, (*i*), 92.

All studies of the use of anticoagulants in myocardial infarction have been criticised in one way or another; in this case because of bias in the allocation of patients to the two groups.† But numerous other studies have given substantially similar results.

The fact that no deaths from hæmorrhage occurred in either group in the above table does not mean that anticoagulant therapy is entirely safe. In other series deaths from hæmorrhage have occurred, and they continue to occur.

It is not known whether heparin given during the interval between starting coumarin group drugs and the development of therapeutic effect (16 to 48 hours) favourably influences the prognosis in myocardial infarction.

---

† TRUELOVE, S. C. (1959) in Medical Surveys and Clinical Trials, edited by L. J. WITTS, Oxford: Blackwell; WRIGHT, I. S., MARPLE, C. D., and BECK, D. F. (1948). *Amer. Heart J.*, **36,** 801.

It has been pointed out that the problem of prophylactic anticoagulant therapy will not be solved if and when the "ideal" anticoagulant is found, because the question is not which anticoagulant to use but rather which patient to treat.*

Acute Coronary Insufficiency, where pain occurs at rest, but where it is uncertain that myocardial infarction has occurred, should probably be treated prophylactically, indefinitely, with an anticoagulant.

Recurrent Venous Thrombosis or Pulmonary Embolism. Patients should probably receive at least 6 weeks anticoagulant therapy.

Retinal Vein or Artery Thromboses are indications for an anticoagulant.

Arterial Thrombosis and Embolism. An anticoagulant may prevent the extension of the clot and possibly hasten re-canalisation. Heparin has a reputation for being the drug of choice in arterial embolism. When an attempt is to be made to convert auricular fibrillation to normal rhythm in any but a case of very recent onset, anticoagulants may be indicated, for they may reduce the chance of embolism, although it is not clear why.

Cerebral Thrombosis or Embolism. There is some evidence that anticoagulants have prophylactic value if given indefinitely, but recovery from an episode is probably not quicker or more complete. It is impossible to dogmatise on which cases should be treated. It is vital to avoid giving anticoagulants to patients who have had a cerebral hæmorrhage.

In Surgery. In vascular surgery anticoagulants may be useful post-operatively, but the risk of increased bleeding is substantial. Patients subject to thrombo-embolism who will necessarily be immobile may be given an anticoagulant starting 24 hours after surgery, but if the operation has been on the central nervous system or the prostate the danger of hæmorrhage is greater and should probably not be risked.

Long-term Anticoagulant Therapy (*ca*)

The decision when to use anticoagulant therapy indefinitely in any patient is difficult. If facilities for adequate control are available it is probably worth while in intelligent co-operative patients who have had a recurrence of myocardial infarction whatever the degree of severity, or a single very severe attack; also in any recurrent thrombotic or embolic disease where the likelihood of further episodes is considered to be substantial and serious.

If adequate facilities for seeing the patient frequently and measuring his prothrombin time are not available, then long-term therapy should not be attempted.

Patients should be stabilised on the chosen drug whilst ambulatory or hospital and prothrombin times should be measured weekly at first after leaving hospital. The patient must be told of the risk of hæmorrhage and of the signs of internal hæmorrhage into the alimentary or urinary tracts. When control has been good for some months the intervals between prothrombin estimations may be extended gradually even up to as long as 8 to 12 weeks.

---

* Schnur, S. J. (1954). *J. Amer. med. Ass.*, **156**, 1127

Safety and good results are only obtainable by very close attention to detail. The optimum dose may be very critical.

In this section a current orthodox view is given, but despite the large number of clinical studies, which have convinced so many of the desirability of long-term anticoagulant therapy, there is still room for the opinion that the benefits of this troublesome treatment remain unproved in coronary artery disease (*6b*).

Contra-indications to Anticoagulant Therapy

These are mostly conditions in which there is a tendency to bleed (*e.g.* blood diseases, hæmorrhoids, ulcerative colitis, hepatic disease), and the contra-indication is relative rather than absolute, the dangers being balanced against the possible benefits. Anticoagulant therapy may be unwise immediately post-operatively, especially after operations on the central nervous system or prostate, in the presence of active peptic ulceration, or severe indigestion, in severe renal disease (hæmaturia is more dangerous in previously damaged kidneys) and in the presence of any abnormality of vitamin K absorption or metabolism (*e.g.* in liver disease).

Anticoagulants increase the chance of embolic phenomena in subacute bacterial endocarditis. The coumarin group of drugs should not be used in the last three months of pregnancy, but anticoagulants may be used in the puerperium. Breast feeding is not a contra-indication. Salicylates inhibit prothrombin formation and so should not be given with any of the coumarin group of drugs, nor should phenylbutazone and perhaps quinine.* Oral antibiotics may perhaps interfere with treatment by reducing vitamin K production by the bacteria in the alimentary tract; liquid paraffin may reduce vitamin K absorption. These possible interfering factors may be of more theoretical than practical importance except when large and prolonged dosage is used.

Surgery in Patients Taking Anticoagulants

It is not necessary to stop the coumarin group of drugs, but the prothrombin time should be at the lower limit of therapeutic effect, that is only about twice the normal. If the prothrombin time is much longer, say 40 seconds, there is serious danger of excessive hæmorrhage. It is undesirable to stop the coumarin anticoagulant altogether before emergency surgery because of the risk of thrombo-embolism following sudden cessation of treatment. Heparin, being short-acting, may be stopped, and started again say 24 hours after operation, or later, depending on the circumstances of the individual case.

---

* Phenacetin or paracetamol may be given to a patient with rheumatism who is on long-term anticoagulant therapy.

Guide to Further Reading on Anticoagulants and Coagulation Defects

(1) Biggs, R. and Macfarlane, R. G. (1957). Human Blood Coagulation and its Disorders. 2nd ed. Oxford: Blackwell.

(2) Jacques, L. B. (1954). Blood clotting and hemostasis. *Ann. Rev. Physiol.*, **16**, 175.

(3) Dacie, J. V., editor (1955). Blood coagulation and thrombosis. *Brit. med. Bull.*, **11**, part 1.

(4) Capeci, N. E., and Levy, R. L. (1959). The influence of anticoagulant therapy on the incidence of thrombo-embolism, hæmorrhage and cardiac rupture in acute myocardial infarction. *Amer. J. Med.*, **26**, 76.

(5) Editorial (1959). Anticoagulants for myocardial infarction. *Brit. med. J.*, (*i*), 838.

(6a) Editorial (1958). Long-term anticoagulant treatment for coronary-artery disease. *Lancet*, (*i*), 417.

(6b) McMichael, J. (1958). *Lancet*, (*i*), 528, and (1959) *Brit. med. J.*, (*ii*), 970.

(7) Rodman, T. *et al.* (1959). A comparative study of four prothrombinopenic anticoagulant drugs. *Amer. J. Med.*, **27**, 411 and 415.

(8) Wright, I. S. (1957). Early use of anticoagulants in treatment of myocardial infarction. *J. Amer. med. Ass.*, **163**, 918.

(9) Russek, H. I., and Zohman, B. L. (1957). Limited use of anticoagulants in acute myocardial infarction. Analysis of 1,000 "good-risk" cases. *J. Amer. med. Ass.*, **163**, 922.

(10) Toohey, M. (1958). Long-term anticoagulant therapy for coronary thrombosis. *Brit. med. J.*, (*ii*), 473.

Chapter 21

PITUITARY AND SEX HORMONES; ERGOT

PITUITARY HORMONES

Those with application in medicine include:

ANTERIOR PITUITARY	POSTERIOR PITUITARY
1. growth hormone	1. vasopressin
2. gonadotrophic hormones	2. oxytocin
3. corticotrophin (p. 88)	
4. thyroid stimulating hormone (p. 365)	

Growth Hormone

Growth hormone preparations from animals have not been effective in treatment of human pituitary dwarfism, and human preparations, though effective, cannot be produced in big enough amounts for routine clinical use.

Gonadotrophic Hormones

Preparations are available from both animals and man. Animal preparations are unsatisfactory, but human chorionic gonadotrophin, obtained from the urine of pregnant women, may sometimes be effective in cryptorchidism. It is useless in oligozoospermia and cannot induce ovulation.

The use of chorionic gonadotrophin in cryptorchidism is controversial (*10*), but is worth trying in boys aged 6 to 9 years provided the testis is not merely retracted and provided it is not ectopic and so incapable of descent without surgical assistance. The selection of suitable cases can be very difficult. The reason why it is undesirable to wait until puberty before acting is that if the testis has not descended by then it may be too late to do anything to permit spermatogenesis to occur. Descent of the testis after chorionic gonadotrophin at age 6 to 9 years settles the point and failure to descend then means that surgery will be needed if the risk of a non-functioning testis is to be avoided. A suitable routine is to give 500 to 1,000 I.U. of human chorionic gonadotrophin, i.m., twice weekly for up to 10 weeks, no longer. Toxic reactions are rare. Some authorities consider that testicular descent during or after such a course is purely coincidental.

Hypopituitarism

In hypopituitarism there is a deficiency of all the hormones secreted by the anterior lobe of the pituitary. The posterior lobe hormones may also be deficient in a few rare cases (*e.g.* when a tumour has destroyed the pituitary). Patients suffering from hypopituitarism may present in coma, in which case treatment is as for a severe acute adrenal insufficiency (p. 95). Maintenance therapy is required, using adrenocortical hormones and thyroid hormone. Sex hormones are not usually required as a routine, although androgens will help to establish a positive nitrogen balance in very wasted patients.

Posterior Pituitary Hormones

Posterior pituitary extract for injection is a sterile aqueous extract of the posterior lobe of animal glands. It contains antidiuretic and oxytocic hormones, both polypeptides. Since the different effects are never required at the same time, the extract has been replaced by separate preparations of the hormones.

Vasopressin (Pitressin)

Vasopressin, the antidiuretic hormone, decreases the amount of water, but not of electrolytes, excreted by the kidney. Secretion of the antidiuretic hormone is stimulated by any increase in the osmotic pressure of the blood supplying the hypothalamus and by a variety of drugs, notably nicotine, and by emotion. Its deficiency leads to the syndrome of diabetes insipidus, characterised by the passing of large amounts of dilute urine and a corresponding thirst and high water intake. In large "unphysiological" doses vasopressin causes contraction of all smooth muscle, raising the blood pressure and causing intestinal colic. The smooth-muscle-stimulant effect provides an example of tachyphylaxis (frequently repeated doses give progressively less effect). It is not only inefficient when used to raise the blood pressure, but it is also dangerous since it causes constriction of the coronary arteries and sudden death has occurred following its use in patients with angina pectoris.

Vasopressin is thus a bad, though official, name for the antidiuretic hormone since only its antidiuretic effect occurs with physiological amounts, and if used to raise the blood pressure it may be lethal.

The sole indication for the use of vasopressin is in the diagnosis and treatment of diabetes insipidus in which it is rational replacement therapy.

Vasopressin is available in sterile aqueous solution for injection; it is digested if given by mouth. The effects of injections of the soluble preparation are so brief that it is not practicable either as therapy or in the diagnosis of diabetes insipidus. Vasopressin tannate in oil is a dep preparation which is given i.m. in doses of 5 I.U., either daily or sometimes only 2 or 3 times a week. A single dose is useful in diagnosis; if the polyuria is due to renal disease there will be no response, but if it is due to either diabetes insipidus or to compulsive water drinking the urinary output will decrease. A snuff made of powdered posterior pituitary is sometimes satisfactory in doses of about 20 I.U., 4 to 6-hourly, but it is not well enough absorbed to control severe cases and may cause ulceration of the nasal mucosa as a result of vasoconstriction.

Oxytocin

Oxytocin stimulates the contractions of the pregnant uterus, which becomes much more sensitive to it at term. The mechanisms governing the initiation of labour are not certainly known, oxytocin may play a part, but patients with diabetes insipidus go into labour normally. Oxytocin is reflexly released from the pituitary following suckling and causes contraction of the myo-epithelium of the breast. The only other clinically important effect is on the blood pressure, which may fall if an overdose is given.

Oxytocin is now increasingly used in the induction of labour but the decision to use it requires special knowledge of obstetrics.

It has been supplanted by ergometrine in the treatment of postpartum hæmorrhage except when, as occasionally happens, there is no response to ergometrine.

SEX HORMONES

Androgens

Testosterone is the natural androgen secreted by the interstitial cells of the testis; it is necessary for normal spermatogenesis, for the development of the male secondary sex characteristics, and for the growth at puberty of the sexual apparatus.

Protein anabolism is increased by androgens, that is androgens increase the proportion of protein laid down as tissue, especially muscle. Growth of bone is promoted, but the rate of closure of the epiphyses is also hastened.

Indications for Androgen Therapy

Testicular failure may be primary, or secondary (due to lack of pituitary gonadotrophins). In either case replacement with androgens is often indicated. Unfortunately, sterility is seldom if ever remedied, although loss of libido and of secondary sex characteristics can be greatly improved. Impotence is helped unless it is due to psychological causes. If androgens are given to a boy with delayed puberty a growth spurt and sexual development will occur. Such treatment is not usually indicated until the age of 10 years, since up to that age natural delay in pituitary secretion may be responsible and normal development may yet occur. In cirrhosis of the liver degradation of œstrogens may be impaired, leading to raised blood levels of œstrogen with feminisation. Androgens may help such patients and also stop the itching of jaundice. Relatively small amounts of androgens can be used to increase the formation of new tissue, *e.g.* in osteoporosis (p. 359). The œstrogen-dependent bony metastases from carcinoma of the breast in premenopausal patients are sometimes made smaller and less painful by very large doses of androgens (100 to 200 mg. methyltestosterone daily), which will always cause marked masculinisation. They may also help in fibrocystic disease of the breast and in some menstrual disorders (*8*).

Preparations of Androgens

Testosterone is not given orally because, although well absorbed from the intestine, it is inactivated by the liver before reaching the systemic circulation. It may be given by subcutaneous implantation of pellets, 6 to 8 of 100 mg. each at approximately 6-monthly intervals. A single large pellet does not give a large enough surface area for absorption.

Methyltestosterone is given as sublingual tablets, 20 to 50 mg. a day in divided doses, or about twice that dose if swallowed.

Testosterone Propionate is given i.m., 25 to 50 mg. 2 or 3 times a week.

Testosterone Œnanthate is given i.m., 250 mg. every 2 or 3 weeks.

Fluoxymesterone is active when swallowed (1 to 5 mg. a day) and may be preferable to testosterone implants. There are various other preparations.

Toxic Effects of Androgens

Unwanted effects are mainly those to be expected of a male sex hormone, increased libido may lead to undesirable sexual activity, especially in mentally unstable patients, and virilisation is obviously undesired by most women. Androgens have a weak salt and water retaining activity which is not often clinically important. Jaundice can occur with methyltestosterone. In patients with malignant disease of bone, *e.g.* metastases from breast carcinoma, androgen administration may be followed by a rise in blood calcium sufficient to produce symptoms. The cause is uncertain. The relatively non-virilising androgens are used to promote anabolism and are discussed on p. 359.

Œstrogens

Œstrone and œstradiol are both natural œstrogens secreted by the ovary. Œstrogens are responsible for the normal development of the female genital tract, of the breast and of the female secondary sex characteristics. The pubertal growth spurt is less marked in females than in males, probably because œstrogens have very much less protein anabolic effect than do androgens, although they are just as effective in promoting closure of epiphyses. Blood œstrogen levels must be above a critical level for the maintenance of both proliferative and (together with progesterone) secretory phases of the uterine endothelium. If the œstrogen level falls too low then the endothelium can no longer be maintained and uterine bleeding follows. Thus uterine bleeding may be stopped temporarily by giving large doses of œstrogens, or may start when they are withdrawn (œstrogen-withdrawal bleeding). Bleeding may occur despite a high blood œstrogen level if large doses are given for a long time, due to infarctions in the greatly hypertrophied endometrium. Œstrogens are necessary for the maintenance of normal pregnancy and for the accompanying breast hyperplasia.

Preparations of Œstrogens

Innumerable œstrogen preparations are available, but the following selection should cover all needs. The dose varies greatly according to whether replacement of physiological deficiencies is being carried out (replacement therapy) or whether œstrogens are being used as drugs to obtain certain effects by pharmacological force (pharmacotherapy). The potency of œstrogens can be measured in women by a method using the occurrence of withdrawal-bleeding as an end point (3).

Œstradiol is a potent natural œstrogen. It is usually given i.m., 1 mg., 2 or 3 times a week, as the monobenzoate (1 mg. stilbœstrol = 0·5 mg. œstradiol monobenzoate). Œstradiol valerate is long-acting, 10 mg. i.m. every 3 to 4 weeks generally being adequate.

Œstrone is probably the principal ingredient of the mixture of equine œstrogens, Premarin. Its advantage is that it has fewer toxic effects than other orally-active œstrogens. (1 mg. stilbœstrol = 0·4 mg. Premarin.)

Ethinylœstradiol is a potent orally active semisynthetic œstrogen. In equipotent doses it is almost certainly not less toxic than stilbœstrol although the contrary is claimed. (1 mg. ethinylœstradiol = 25 mg. stilbœstrol.)

Stilbœstrol was the first synthetic œstrogen made and it is still the most generally useful on grounds of efficacy and low price. However, if more than 1 mg. a day is given, it is liable to cause nausea, vomiting and other abdominal disturbances, and headache.

Other Synthetic Œstrogens. Hexœstrol and dienœstrol are not less toxic than stilbœstrol in equipotent doses (1 mg. stilbœstrol = 4 mg. dienœstrol = 20 mg. hexœstrol). Other œstrogens are chlorotrianisene (TACE) and methallenœstril (Vallestril).

Indications for Œstrogen Therapy

Replacement Therapy in Hypo-ovarian Conditions. 2 mg. stilbœstrol may be given orally, daily, for 20 days and repeated after a 10-day interval, or, if withdrawal bleeding occurs, on the fifth day of the cycle. Unless the cause of the hypo-ovarian state is primary ovarian failure treatment should be stopped after every third cycle to see if spontaneous menstruation will occur.

For Climacteric Symptoms (*1*) severe enough to demand treatment there are three rules that should be followed:—

1. The minimal effective dose should be given.
2. Treatment must be in interrupted courses and not continuous.
3. Treatment should be stopped as soon as possible.

Stilbœstrol, 0·2 mg. orally, daily, may be tried first for 28 days. If menstruation is still occurring the œstrogen administration should be integrated with the periods and stopped when bleeding begins, otherwise an interval of 10 to 14 days during which no œstrogen is given should follow each cycle of administration. If symptoms were relieved when taking the stilbœstrol but returned when it was withdrawn, the second course should consist of the same dose, but if they did not recur on withdrawal the second 28-day course may be 0·1 mg. stilbœstrol daily. If symptoms were not relieved the dose may be increased, but it is seldom necessary to give as much as 1 mg. a day, a dose with which withdrawal bleeding may be expected.

Treatment may have to last anything from a few months to a few years.

For patients who fail to respond to the above régime, who relapse repeatedly or have withdrawal-bleeds at low doses, œstrogen-androgen mixtures may be tried (*e.g.* Femandren, Mepilin, Mixogen, and there are many others), according to the above time schedule, but facial hair may appear.

Continuous œstrogen treatment is undesirable as it will cause troublesome bleeding and also there is a theoretical risk of carcinogenesis.

Pharmacotherapy:—

Menstrual Disorders. Cyclical administration of œstrogens with or without a progestogen is used in secondary amenorrhœa and for prolonged or irregular menstrual bleeding (*e.g.* in metropathia hæmorrhagica). Such uses, except perhaps the deliberate production of withdrawal bleedings to provide psychological benefit, demand considerable skill combined with knowledge of menstrual physiology if they are to be beneficial.

Dysmenorrhœa usually only occurs, in the absence of complicating disease, in cycles in which ovulation takes place. Suppression of ovulation may prevent the pain and may be accomplished by giving 1·5 to 2 mg. stilbœstrol orally daily from the third day of the cycle for 20 days. It is probably inadvisable to suppress ovulation for more than three consecutive cycles lest it be not spontaneously re-established. This treatment should only be used in the most severe cases who have failed to respond to other measures. Non-narcotic analgesics coupled with a suitable psychological approach are usually sufficient.

Vaginitis. Senile vaginitis usually responds to daily insertion of a stilbœstrol pessary (0·1 to 0·5 mg.). Œstrogen ointment can be used in small girls with vaginitis.

Suppression of Lactation. It is said that œstrogens prevent the engorgement and pain in a breast in which inhibition of lactation is occurring due to absence of suckling. They do not themselves actually suppress lactation, which will occur despite them if suckling is allowed. A usual technique is to give stilbœstrol thus:—

5 mg.	orally	three	times	daily	for	three	days
,,	,,	twice		,,	,,	,,	,,
,,	,,	once		,,	,,	,,	,,
1 mg.	,,	three	,,	,,	,,	,,	,,
,,	,,	twice		,,	,,	,,	,,
,,	,,	once		,,	,,	,,	,,

This sometimes fails and a single injection of a long-acting œstrogen-androgen mixture (*e.g.* Primodian-Depot) immediately after labour is claimed to give satisfactory results in most cases, but it has not yet undergone the stringent test of years of routine use that has been the lot of stilbœstrol.

Hormone-dependent Carcinoma. High doses of œstrogens are used in prostatic carcinoma, which is an androgen-dependent neoplasm. Ethinylœstradiol, 3 mg. daily, or an equivalent dose of stilbœstrol, if it is tolerated, is used. Feminisation is inevitable and the gynæcomastia is often painful.

Inoperable breast carcinoma in post-menopausal women may also sometimes be favourably influenced temporarily by œstrogens.

Post-menopausal Osteoporosis (p. 359) may respond to œstrogen therapy.

To Reduce Sexual Urge in men prone to commit socially unacceptable sexual acts is an occasional indication for œstrogens. 1 to 2 mg. stilbœstrol daily should be enough.

Blood Cholesterol Reduction can sometimes be achieved by œstrogens on the, at present, rare occasions when there is a definite indication to attempt it.

Unwanted Effects of Œstrogens

These consist chiefly in an excess of feminisation. Withdrawal-bleeding is common, but seldom prolonged. In men reduced libido, impotence and gynæcomastia which may be painful occur, and there is sometimes salt and water retention with œdema.

Oral administration is liable to cause nausea, vomiting and diarrhœa. Hypersensitivity phenomena are rare.

Progesterone and Progestogens

Progesterone is produced by the corpus lutem and converts the uterine epithelium from the proliferative to the secretory phase. It is thus necessary for implantation of the ovum, and is essential throughout pregnancy, in the last two-thirds of which it is secreted in large amounts by the placenta.

The production of powerful synthetic progestogens and knowledge of the amounts secreted in the body has led to the realisation that progesterone has often been administered in the past in inadequate amounts. The decision when to use progestogens is a skilled one and therapeutic effects are uncertain. A detailed account of what can be attempted is beyond the scope of this book.

The clinical uses of progestational agents are ill-defined; the principal indication is threatened and habitual abortion. There is, however, no proof that they are beneficial. Very rarely infertility is caused by progesterone insufficiency and then replacement therapy is indicated.

Other proposed uses have included menstrual disorders, the premenstrual syndrome, endometriosis, and dysmenorrhœa.

In animals progesterone can inhibit ovulation when used appropriately. Synthetic compounds have therefore been made in an attempt to produce an oral contraceptive for human use. Clinical trials have taken place in Puerto Rico and success has been reported amongst subjects who adhered carefully to the daily schedule of administration. Similar trials are now being done in Britain.

The requirements for a contraceptive that can be applied generally are stringent, for it must be cheap, convenient to take, efficient and safe. So far no substance with all these properties has yet been found although there can be little doubt that it will be, when social and moral, rather than pharmacological, considerations will control its use.

The following progestogen preparations are available: progesterone given i.m. in an oily solution, as microcrystals or as pellets implanted s.c. Alternatively dimethisterone, ethisterone, norethisterone, norethynodrel (Enavid)* and Primolut depôt can be used, and there are many others.

---

* Also contains ethinylœstradiol.

Protein Anabolic Agents

Androgens are effective protein anabolic agents, but their clinical use for this purpose is limited by their capacity to cause virilisation. Partially successful attempts have been made to produce compounds with the desired anabolic action but without the other effects. These have resulted in the production of methandriol (Protandren, Stenediol), methylandrostanolone (Androstalone), norandrostenolone (Durabolin) and norethandrolone (Nilevar). These compounds can be used instead of the ordinary androgens in the treatment of osteoporosis. They can also prevent the calcium and nitrogen loss in the urine that occurs in patients bedridden for a long time and they have therefore been recommended in the treatment of some severe fractures. Growth in hypogonadal children is at first stimulated and the anabolic steroids may be worth using in some cases of dwarfism. A large dose may cause premature epiphyseal fusion and therefore prevent the attainment of normal adult stature.

Their use in acute renal failure to reduce catabolism is rational and may yet prove to be effective in reducing the need for hæmodialysis.

The use of anabolic steroids in conditions of general wasting is justifiable in extreme cases such as severe ulcerative colitis, and in the later stages of malignant disease they may make the patient feel and look less wretched.

The itching of jaundice may be relieved and these drugs are perhaps preferable to testosterone for the purpose. There is, however, a risk of increasing the degree of jaundice.

Attempts have been made to use anabolic steroids to counter the unwanted catabolic effects of adrenocortical hormones when the latter are used over long periods, but such therapy is still experimental.

None of these substances can be assumed to be quite free from virilising properties in high doses; acne and greasy skin may be the early manifestation of virilisation. Liver damage may occur, but it is usually mild and reversible. If used in carcinoma of the breast with bone metastases there may be hypercalcæmia, as with testosterone.

It will be evident from the outline above that the indications for use of the anabolic steroids are still the subject of discussion. No dogmatic statements are justifiable and they should be given with great caution until much more is known. Their casual use as general tonics is quite unjustifiable.

Œstrogens have only a modest anabolic effect.

Osteoporosis

Apart from treatment of the cause, androgens or œstrogens are given according to whether there are clinical suggestions of a lack of one or the other. Alternatively the anabolic agents discussed above may be used.

Some patients react better to a combination of androgen and œstrogen than to either given alone, *e.g.* stilbœstrol, 0·5 to 1 mg., with methyltestosterone, 10 to 30 mg., daily by mouth, or one of the proprietary mixtures, although these have the disadvantage that the dosage of one hormone cannot be varied independently of the other. It should be recalled that when substantial œstrogen dosage is used in women administration should be cyclical, about 4 weeks on and one week off; there is likely to be withdrawal-bleeding, which some postmenopausal women find gratifying, but others objectionable.

ERGOT

> "He gently prevails on his patients to try
> The magic effects of the ergot of rye."
>
> (attributed to Alfred, Lord Tennyson)

Ergot is a fungus which lives on grasses, especially rye. For medical purposes the fungus is produced by artificial infection of the plant.

The history of ergot is famous, for consumption of bread made from infected rye has caused epidemics of painful gangrene of the extremities, due to its vascular effects. The disease was called St. Anthony's Fire because sufferers obtained relief by visiting the saint's shrine, no doubt chiefly because they had left the area where contaminated grain was being used. Fits and mental disorder were also a feature of these epidemics, but it is not known whether these were partly due to concurrent nutritional deficiencies.

Ergotism is now very rare but an epidemic was reported in England (Manchester) in 1928* and in France in 1951†, although the genuineness of both these has been questioned.

The Discovery of the Constituents of Ergot (ergotamine, ergotoxine, and ergometrine‡) presents an interesting chapter in the history of both pharmacology and therapeutics. At the beginning of this century pharmacologists investigated ergot and found ergotamine, a principal alkaloid, ergotoxine, later found to be a mixture of three alkaloids, and histamine, acetylcholine and tyramine amongst other things. Ergometrine was found in 1935. The ergot alkaloids are all derivatives of lysergic acid. Before 1935 some clinicians maintained that the uterine activity of ergot extracts was not all accounted for by the known constituents, and their view was supported by the fact that the then current pharmacopoeial method of preparing the extracts effectively removed the known orally active substances. In 1932, a newly formed Pharmacopoeial Committee decided that it was time that they either stopped the elimination of the active principles or else found out what unknown substance was rendering the extracts active, if indeed they were active. The Committee invited Chassar Moir to investigate the subject for them.

---

* Robertson, J., and Ashby, H. T. (1928). *Brit. med. J.*, (*i*), 302

† Gabbai *et al.* (1951). *Brit. med. J.*, (*ii*), 650 and editorial, *ibid.*, 506

‡ Also called ergonovine.

Moir prepared an extract exactly in accordance with the Pharmacopœial regulations, *i.e.* it should, according to current knowledge, have been inert. He administered it to parturient patients and recorded the results with a balloon in the uterus attached to a manometer. "It was with the greatest surprise I found that, far from being inert, this preparation surpassed by great measure the activity of any drug which I had previously used in the same manner." He also observed that the rate of onset and type of contractions differed from those characteristic of ergotoxine and ergotamine. Moir could only suppose that the effects he observed were due to an entirely new constituent of ergot and that those "ergot alkaloids hitherto supposed to be all-important, play in reality but subsidiary part in the clinical activity of the drug." Sir Henry Dale, whose early work on the analysis of the constituents of ergot is a pharmacological classic, commented on Moir's discovery. He wrote that another chapter had been opened "and probably one of great importance, in the already complicated story of ergot and its active principles. . . . Those acquainted with the present position, and its development during a quarter of a century, may be inclined to regard Dr. Moir's observations as a rebuke to the presumption of laboratory pharmacologists. They do, indeed, emphasise the danger of basing therapeutic conclusions on laboratory data, without direct clinical evidence. It is only fair to state, however, that the present position has arisen, not in spite of such evidence as Dr. Moir now supplied, but for lack of it. The need has been recognised and urged by some of us throughout the period in question; but, without such direct experimental guidance from the clinic, we could only search for the principles in ergot producing certain well-defined effects in the laboratory, and hope for the proper clinical trial of the substances so identified. . . . I have, indeed, on more than one occasion endeavoured to get a proper experimental comparison made in the clinic. . . . More than one eminent gynæcologist was willing to carry out a test; but only by handing the extracts to a resident officer or ward sister, with an instruction to administer them to alternate patients as a routine and to record impressions of their respective values. It can safely be stated that, so far from affording data for a quantitative comparison, such a method would not even give trustworthy information as to whether either extract was active at all." X . . . and Y . . . in the case of an extract of ergot "were content to show that the ward sister could not distinguish its action from that of a 'Marmite' solution, when both were given to alternate patients in the puerperium. The inference was that the liquid extract had no action, but Dr. Moir's experimental records show it to contain what may well prove to be the most important substance in ergot from the point of view of practical therapeutics." This prediction was correct for the substance was ergometrine.

Fortunately Moir's paper was published in a journal which has a correspondence column so that the subsequent clash of opinion between clinician and pharmacologist could take place in public.*

The Actions of Ergot

Ergotoxine is obsolete in therapeutics and so only ergotamine and ergometrine and some derivatives will be considered here.

Ergot alkaloids have the following actions:—

a. Uterine Effects

Ergometrine is now the only ergot alkaloid used for stimulating uterine activity, as ergotamine is slow in acting even after i.v. injection, whereas ergometrine acts immediately when injected and in a few minutes after oral administration. It is also relatively free from serious circulatory side-effects. The uterus is stimulated at all times, but is much more sensitive in late pregnancy.

Ergometrine and oxytocin differ in their actions on the uterus. In moderate doses oxytocin produces slow generalised contractions with complete relaxation in between and ergometrine produces faster contractions superimposed on a tonic contraction. Both substances in high dose produce sustained tonic contraction. It will be seen, therefore, that oxytocin is more suited to induction of labour and ergometrine to the prevention of post-partum hæmorrhage, the incidence of which is reduced by its routine use. An injection of ergometrine (0·3 to 0·5 mg. of the maleate) acts on the uterus for at least 3 hours. It may be given i.m., with or without hyaluronidase, or i.v.

The timing of the injection is the subject of disagreement. It is commonly given when the anterior shoulder of the child is delivered, but some give it earlier at the crowning of the head (never before this) or later when the placenta has separated or has been delivered. Ergometrine tablets may be given orally (0·5 to 1 mg. of the maleate) twice a day in the early puerperium if bleeding occurs, or with incomplete abortions.

The occurrence of hypertension, lasting hours or even days after ergometrine has been given is recognised but not fully investigated. The incidence of this effect may be less with methylergometrine. It may be that in some patients the ergometrine is capable of inducing vascular effects of a magnitude similar to those of ergotamine.

---

* Moir, C. (1932). *Brit. med. J.*, (*i*), 1119, 1189, and (*ii*), 75.

b. Vascular Smooth Muscle Constrictor Effects

This is the most prominent effect of ergotamine. Spasm of the arterioles occurs, with hypertension and reduced peripheral blood flow. The duration of action of a single dose may exceed 24 hours so that if the drug is being given several times a day for, say, migraine (p. 155) there is a short-term cumulation which can be dangerous. Stimulation of other smooth muscle occurs but is of little clinical importance.

c. Adrenergic Blocking Effects

This is antagonistic to the vasoconstrictor effect mentioned above. It is negligible with ergometrine and moderate with ergotamine, although insufficient to prevent severe vasospasm. This action is increased by hydrogenation which also reduces oxytocic and vasoconstrictor activity.

Hydrogenated alkaloids of ergotoxine are available (Hydergine, a mixture of dihydroergo-cryptine, -cristine and -cornine). Hydergine is given sublingually, 0·5 to 5 mg. daily, in divided doses; or 0·3 to 1 mg., s.c., or i.m. It is occasionally used as a peripheral vasodilator but may be effective in some cases of migraine despite this.

d. Central Nervous System Effects

These are ill understood. There is a general depressant effect which includes the respiratory and vasomotor centres. Hypotension may occur. The vomiting centre is stimulated, probably via the nearby trigger zone. Cardiovascular reflexes are inhibited by a central action and this is perhaps more important as a cause of postural hypotension than is the adrenergic blocking effect.

Toxicity of Ergot Alkaloids

Nausea and vomiting are very prominent and often limit the use of ergot derivatives. Peripheral gangrene has frequently been reported from the excessive use of ergotamine in migraine, especially in cases of hepatic disease. This alkaloid is especially dangerous in patients with existing obliterative vascular disease. The gangrene may not be entirely due to vasoconstriction but also to concurrent damage to the lining of small vessels with resulting thrombosis, as thrombophlebitis unrelated to the site of administration sometimes occurs after ergotamine. Angina pectoris may occur. The blood pressure may rise or fall. Patients complain of coldness and paræsthesiæ, weakness and muscular pain. Confusional states, depression, convulsions, hemiplegia and other neurological syndromes have been recorded following overdosage.

Metabolism of all the alkaloids is in the liver.

Guide to Further Reading on Sex Hormones

(*1*) Swyer, G. I. M. (1959). The œstrogens. *Brit. med. J.* (*i*), 1029.
(*2*) Swyer, G. I. M. (1960). Progestogens and their clinical uses. *Brit. med. J.*, (*i*), 48 and 121.
(*3*) Bishop, P. M. F., Kennedy, G. C., and Wynn-Williams, G. (1948). Potency and "toxicity" of some synthetic œstrogens. *Lancet*, (*i*), 764.
(*4*) Editorial (1958). Œstrogens in osteoporosis. *Brit. med. J.*, (*i*), 1051.
(*5*) Watson, R. N., *et al.* (1959). A six-month evaluation of an anabolic drug, norethandrolone, in underweight persons. *Amer. J. Med.*, **26**, 238 and 243.
(*6*) Foss, G. L. (1959). The less virilising androgens. *Practitioner*, **182**, 235.
(*7*) Smith, M., *et al.* (1959). The newer steroids. *Practitioner*, **183**, 519.
(*8*) Swyer, G. I. M (1956). The use of androgens in the female. *Lancet*, (*ii*), 433.
(*9*) Annotation (1959). Androgen therapy. *Brit. med. J.*, (*i*), 1400.
(*10*) Editorial (1957). Cryptorchism. *J. Amer. med. Ass.*, **163**, 650.

Chapter 22

THYROID HORMONES AND ANTITHYROID DRUGS

THYROID HORMONES

Dried thyroid, thyroxine (tetra-iodothyronine) and tri-iodothyronine* are all iodine-containing compounds effective in the treatment of hypothyroidism (cretinism or myxœdema). Thyroid hormone is stored in the gland as thyroglobulin from which thyroxine and tri-iodothyronine are released and in addition thyroxine may be converted into tri-iodothyronine in the peripheral tissues. For convenience the term thyroid hormone is used to cover both tri-iodothyronine and thyroxine. They circulate in the blood in loose combination with protein.

The Mode of Action of Thyroid Hormone is not known. It accelerates cellular oxidation, which increases the basal metabolic rate. Thyroid hormone is necessary for growth and all cells need it if they are to function properly.

The Thyroid Stimulating Hormone (TSH) of the anterior pituitary controls the release of thyroid hormone and also the uptake of iodide by the thyroid gland. TSH secretion is inhibited by a high level of thyroid hormone in the blood and stimulated by a low level; thus there is a "feed-back" mechanism of control. TSH is sometimes used in the differentiation of myxœdema due to thyroid disease from that due to hypopituitarism. The ^{131}I uptake by the thyroid is measured after three daily injections of 10 units of TSH. If the myxœdema is due to primary thyroid disease there will be no change, but if the pituitary is responsible then the ^{131}I uptake will increase.

Exophthalmos is *not* due to excess of thyroid hormone, but possibly to excess of pituitary TSH. Thus treatment of severe exophthalmos with dried thyroid (120 to 180 mg. daily) is reasonable and sometimes effective, probably by "turning off" the pituitary. Exophthalmos may be made worse by any of the treatments for thyrotoxicosis. Thyrotoxic patients with marked exophthalmos should be treated with small amounts of antithyroid drugs: enough to make the symptoms bearable, but not enough to make the patient completely euthyroid. Exophthalmic ophthalmoplegia may require irradiation of the pituitary or surgical decompression of the orbit in an attempt to preserve vision.

Indications for Thyroid Hormone are cretinism and myxœdema.

---

* Official name, liothyronine.

Early treatment of cretinous babies gives excellent results and must be continued throughout life. If treatment is delayed irrecoverable mental deficiency may occur. Myxœdema due to panhypopituitarism requires replacement with adrenocortical as well as with thyroid hormone. Small doses of thyroid in normal subjects merely depress TSH production and consequently reduce the output of thyroid hormone by an equivalent amount. Thus thyroid hormone may be tried in young patients with sporadic simple goitre, which is presumably due to excess TSH. This often reduces the size of the goitre, with consequent cosmetic improvement.

Thyroid hormone should never be used in cases of simple obesity, if enough is given to "burn up" the excess fat, then other symptoms of hyperthyroidism are inevitable and appetite is stimulated, also it may lead to addiction to thyroid.

Preparations and Dosage of Thyroid Hormones

Thyroid Tablets, B.P., are a preparation of the dried gland of ox, pig or sheep. The initial dose is 30 to 60 mg. daily. In the old and patients with heart disease or hypertension this should be reached gradually, starting with 15 mg. daily for the first week and 30 mg. for the second. The dose is then increased by 30 mg. every fortnight until symptoms are relieved; doses over 240 mg. daily are seldom required. The maximum effect of a dose does not occur for about 10 days and passes off over 2 to 3 weeks. A cretinous baby should be given 15 mg. daily at first; this may be increased by 15 mg. fortnightly. Some diarrhœa and loss of weight are common when cretins are first treated, but perseverance is essential. The maintenance dose must be adjusted for each patient according to the clinical response.

Thyroxine Sodium is available as a pure substance, is effective orally, but can if necessary be given parenterally. It is reliable and is replacing the crude preparation. 0·1 mg. thyroxine sodium is approximately equivalent to 60 mg. of dried thyroid.

Tri-iodothyronine is the most rapidly effective thyroid hormone, a single dose giving maximum effect within 24 hours and passing off over about a week. Its main use is in myxœdema coma, which is rare. The dose in this condition is 0·1 mg. parenterally (it is as effective orally), repeated 4 to 12-hourly according to the state of the patient. Heart failure and death are very common during treatment of myxœdema coma, but death is inevitable in the absence of treatment. The acetic acid analogue of tri-iodothyronine, triac, is similar but less potent.

Side Effects of Thyroid Hormones parallel the increase in basal metabolic rate. The symptoms and signs are those of thyrotoxicosis, but exophthalmos does not occur. Angina or heart failure are liable to be provoked by too vigorous thyroid therapy; should they occur thyroid must be discontinued for at least a week and only started again at lower dosage.

ANTITHYROID DRUGS

Drugs used for the treatment of hyperthyroidism include:

1. **Iodide,** an excess of which reduces the production of thyroid hormone temporarily by an unknown mechanism.[*]
2. **Thiourea Derivatives and Perchlorate** which block the synthesis of thyroid hormone.
3. **Radio-active Iodine** which destroys the cells making thyroid hormone.

Iodide

Iodide is well absorbed from the intestine, is distributed like chloride or bromide in the body and is rapidly excreted by the kidney, unlike bromide. It is selectively taken up and concentrated by the thyroid, more in hyperthyroidism and less in myxœdema. A deficiency of iodide reduces the amount of thyroid hormone produced, this stimulates the pituitary to secrete TSH, and compensating hyperplasia and increased vascularity of the thyroid result, with eventual goitre formation.

Some foods, such as plants of the cabbage family, contain substances which block uptake of iodide by the thyroid or prevent its incorporation in thyroid hormone; these may be a factor in endemic goitre.

Goitre is endemic in Tasmania, and in 1949 potassium iodide was given prophylactically to the schoolchildren. However, five years later the incidence of goitre was found to have slightly increased, and to have coincided with the introduction of free school milk. This greatly increased demand for milk had led the local farmers to grow a special hardy kale for cattle food. It seems likely that the increased goitre in children was due to a goitrogen in the milk from cattle fed on this kale, which was more than enough to reverse the benefits of prophylactic iodide.[†]

An excess of iodide has opposite effects to those of TSH on the thyroid; iodide promotes involution, making the gland smaller, firmer, and less vascular, so that surgery is easier. This is easy to understand where the hyperplasia is due to iodide deficiency (added iodide allows thyroid hormone synthesis, and "turns off" TSH), but how it works in thyrotoxicosis is not known.

Indications for Iodide Therapy

Iodide is used before operation on thyrotoxic patients. Even in a thyrotoxic patient potassium iodide (300 mg. daily) reduces the hyperplasia and vascularity of the gland; symptoms are also greatly improved. This effect is maximal after 10 days' treatment and then declines so that symptoms tend to recur in the absence of another antithyroid drug.

---

[*] Patients taking iodide as an expectorant rarely develop a goitre or myxœdema.

[†] CLEMENTS, F. W., and WISHART, J. W. (1956). *Metabolism*, **5**, 623.

Thyroid Crises are rare with modern methods of preparing thyrotoxic patients for operation, they are due to liberation of large amounts of thyroid hormone into the circulation. Treatment is by potassium iodide 1 to 2 G. daily, i.v. if necessary, glucose to replace the calories used, the B vitamins, continuous oxygen, sedation, and cooling if pyrexia is extreme.

Prophylactic Iodide (1 part in 100,000) should be added to all the salt used in areas where goitre is endemic. In Michigan, U.S.A., the incidence of goitre was inversely proportional to the iodide content of the water supply. In one county 42% of 3,645 schoolchildren had goitre in 1924. Four years later after propaganda for prophylactic iodide incidence of goitre among children in one town of that county dropped to 9%. Of the 900 children in the town who had used only *iodised* salt, one had a goitre; of 84 using mainly *ordinary* salt, 11 had goitres (3).

A Small Goitre presumed due to iodine deficiency (a presumption justifiable only in an area of endemic iodine deficiency) which is not producing symptoms may involute if potassium iodide, 50 mg. daily, is given, but nodularity or increase in size of the goitre is an indication for surgery.

Granulomatous Lesions of late syphilis and actinomycosis used to be treated, with some benefit, with very large doses of iodide. Antibiotics usually give better results.

As an Antiseptic for use on the skin Iodine Solution, Weak, B.P., is very effective.

Bronchial Secretion is greatly increased by large doses of iodide, probably by a reflex induced by its gastric irritant effect; tolerance occurs but is clinically unimportant. Iodide is excreted in the bronchial mucus but it is not known whether or not this helps to liquefy sputum. It is used to loosen the sputum of chronic bronchitis and asthmatics, but must be given to the limits of tolerance. There is no point in including small amounts in cough mixtures. For its use, see p. 216.

Lugol's Solution is a traditional preparation which contains 5% iodine and 10% potassium iodide in water. The dose is 0·5 ml. 3 times daily. Potassium iodide, 150 mg. daily, is just as effective, as the iodine of Lugol's solution is converted into iodide before it is absorbed.

Organic Compounds Containing Iodine are widely used as contrast media in radiology. Oily solutions are used, for example, in myelography, retrograde pyelography and bronchography; some solutions liberate iodine so that it is essential to ask patients specifically whether they are sensitive to it before they are used. A few preparations do not contain iodine. For intravenous pyelography water-soluble iodine compounds rapidly excreted by the kidney are used. The biliary system can be outlined by oral or i.v. administration of compounds excreted in the bile. The iodine in these water-soluble compounds is firmly bound, but patients are sometimes hypersensitive to them. An i.v. test dose of 50 micrograms ought always to be given half an hour before the full i.v. dose.

Toxic Effects of Iodine

Patients vary enormously in their tolerance of iodine, some are hypersensitive to it both orally and when put on the skin. Symptoms of iodism are similar to those of bromism and include a metallic taste, excessive salivation with painful salivary glands, running eyes and nose, sore mouth and throat, a productive cough, diarrhœa, and various rashes which may mimic chicken-pox. The iodine solution used in antisepsis is caustic; it is sometimes drunk by suicidal patients: stomach washouts with solutions of starch are an antidote.

Thiourea Derivatives

Thiourea derivatives do not block uptake of iodide by the thyroid but they do block the incorporation of iodine into organic precursors of thyroid hormone. The amount of hormone produced is thus reduced, and thyrotoxic patients correspondingly benefitted. Unfortunately the reduction in circulating thyroid hormone sometimes induces the pituitary to produce more TSH, which in turn causes thyroid hyperplasia and increase in vascularity. TSH may also make the thyrotoxic eye signs worse.

History of the Discovery of the Antithyroid Thioureas

The association of endemic goitre with hypothyroidism had long been known and there was a supposition that the goitre might represent an attempt by the body to overcome this. It had also been suggested that any agent capable of causing this sort of goitre might be useful in the treatment of hyperthyroidism.

In 1932 it was suggested that a cyanide radical might be responsible for the goitre that had been shown to occur, a few years previously, in rabbits fed on cabbage. Ten years later it was noticed that patients treated with thiocyanates (for hypertension) developed goitre, and so thiocyanates were tried on some hyperthyroid patients, but without useful therapeutic effect.

The discovery of the antithyroid activity of thiourea in the 1940's resulted from a variety of further observations. One group of research workers found that the goitrogenic factor in rape-seed was probably allythiourea, others, examining the relationship between taste and toxicity in rats, happened to choose the bitter substance phenylthiourea, and found it to be goitrogenic. Yet others noted that workmen manufacturing sulphathiazole, and rats dosed with sulphaguanidine, developed goitres.

Inspired by these observations two independent groups simultaneously discovered that thiourea was a potent and relatively non-toxic goitrogenic substance. It was, with thiouracil, soon given a clinical trial in hyperthyroidism and found effective (*1*). Numerous other drugs have followed it, some being substantially safer.

Thiourea thus introduced in 1943 was in fact being re-introduced into medicine. Half a century previously it had been advocated and used to reduce lupus scars and in arthritis, leprosy and deafness. Its toxicity and therapeutic inefficacy for these purposes led to its abandonment 20 years later, with its ability to prevent thyroxine formation and to cause goitre still undetected.

Toxic Effects of Thiourea Derivatives

These drugs are all liable to cause hypersensitivity effects: rashes, and most serious of all, leucopenia sometimes proceeding to agranulocytosis or aplastic anæmia. Blood dyscrasias are most common in the first month of treatment. Repeated leucocyte counts are often advocated, but agranulocytosis may be so acute that the counts give no warning (see p. 447). If a pregnant or lactating woman is thyrotoxic she should be treated with the *smallest possible* amount of these drugs because they cross the placenta and are also excreted in the milk. Goitre is more common in the young than in the old as the latter are less responsive to TSH.

Preparations and Dosage of Thiourea Derivatives

The doses given are for the average thyrotoxic patient, but in a very severe thyrotoxic who may die of the disease three times as much may be given. All are taken by mouth in divided doses. After about a year they may be withdrawn to see if a remission has occurred.

There is little to choose between the following:—

Propylthiouracil. The initial dose is 400 mg. daily; after 8 weeks this is reduced to a maintenance dose of about 100 mg. daily. Thiouracil and methylthiouracil are obsolete.

Carbimazole (Neo-Mercazole). The initial dose is 40 mg. daily for about 8 weeks, the maintenance dose is about 5 to 30 mg. daily. It is probably the safest of the thiourea derivatives, but not safer than perchlorate.

Preparation of a Hyperthyroid Patient for surgery can be satisfactorily achieved by making him euthyroid with carbimazole (40 mg. a day) for 1 to 2 months and then adding Lugol's iodine for 7 to 10 days to reduce the inconvenient vascularity of the gland. Perchlorate cannot be used instead of carbimazole for this purpose, as administration of the iodine to reduce vascularity would result in relapse.

Perchlorate

Perchlorate blocks the synthesis of thyroid hormone by preventing the uptake of iodide by the thyroid. Toxic effects other than rashes are uncommon. It is given as potassium perchlorate; initially 1,600 mg. daily in divided oral doses, after 8 weeks this is reduced to a maintenance dose of 200 to 800 mg. daily. The effects of perchlorate are antagonised by iodide.

Radio-active Iodine (^{131}I)

^{131}I is treated by the body just like the ordinary non-radio-active isotope, so that when given by mouth as iodide it is concentrated in the thyroid gland. It emits mainly β radiation which penetrates only a few millimetres of tissue and thus allows therapeutic effect on the thyroid without damage to the surrounding structures; however, it also emits a few γ rays, which are relatively penetrating and can be detected with a Geiger counter. These can be used in tests of thyroid function. After administration of ^{131}I in thyrotoxicosis the count over the thyroid is abnormally high, in myxœdema abnormally low. The percentage uptake at 24 hours may be measured, or alternatively the count may be compared with that over an inert area, such as the thigh, and the result expressed as a ratio (neck/thigh ratio). This test will not detect mild myxœdema but is very sensitive in diagnosis of thyrotoxicosis. Abnormally situated thyroids can be located using ^{131}I. ^{131}I has a half life of 8 days, and even the small amount used for diagnostic purposes is enough to be an appreciable radiation hazard to children. It should not be used during pregnancy or lactation when ^{132}I with a half life of only a few hours can be used.

^{131}I is used in the treatment of certain cases of thyrotoxicosis and in combination with surgery in some cases of thyroid carcinoma, especially those in which metastases are sufficiently differentiated selectively to absorb iodide. The beneficial effects of a single dose may be felt in one month but its action is not complete for 3 months.

Treatment of Thyrotoxicosis

A very mild case, especially if following some shock or unusual stress, may be followed for a few months without treatment in the hope that a spontaneous remission will occur. Sedation is usually given, but probably does no good. For more severe or long-standing cases there are three possible lines of treatment, each with its special advantages and disadvantages:—

1. Sub-total thyroidectomy, after preparation with antithyroid drugs
2. Antithyroid drugs alone
3. Radio-active iodine

Sub-total Thyroidectomy

Disadvantages of Operation are:—

a. Mortality (in highly skilled hands less than 0·1%)
b. Risk of tetany and laryngeal paralysis
c. Risk of myxœdema (about 5%)
d. Risk of recurrence (about 5%)
e. Some patients cannot be made fit for a major operation

The chance of myxœdema can only be diminished (by less extensive resection) at the price of an increased recurrence rate and vice versa.

Advantages of Operation are:—

a. Most patients are cured by a single operation, no further treatment being required
b. Risk of malignancy is removed
c. Most patients get a good cosmetic result; they have an unsightly lump replaced by a comparatively easily hidden scar

Clear indications for operation include: evidence or likelihood of obstruction to trachea or veins, nodularity of the thyroid (with its increased risk of malignancy), any clinical grounds for suspecting malignancy, failure of medical treatment and residence where long-term supervision is impossible.

Antithyroid Drugs as Sole Treatment

Disadvantages include:—

a. Treatment must be prolonged, with supervision at frequent intervals
b. Agranulocytosis, or aplastic anaemia, may be fatal
c. Only about half the patients can stop treatment after a year
d. Increase in size of the thyroid, which is unsightly and may be dangerous if it produces obstructive symptoms
e. Unsuspected malignant change may have occurred
f. In animals these drugs have induced carcinomata, but not so far in man

Advantages include:—

a. No operation, with its attendant risks
b. Can be used in patients unfit for surgery

c. Less risk of myxœdema (which improves anyway when drugs are stopped)
d. If a remission does not occur after a year's treatment, then surgery can still be performed

Radio-active Iodine in Thyrotoxicosis

Disadvantages include:—

a. Risk of inducing malignant disease or mutations
b. Dose is difficult to judge, therefore more than one treatment often needed
c. Risk of myxœdema if a slight overdose is given
d. Slow in action

Advantages include:—

a. No operation with its attendant risks
b. Only one to four treatments needed
c. Very easy for the patient; like drinking a glass of water
d. Can be used for patients unfit for operation
e. Can be used when other treatments have failed
f. Mortality nil

The factor which has limited the therapeutic use of ^{131}I is undoubtedly the theoretical risk of inducing carcinoma. This is obviously more serious in young patients. ^{131}I is the treatment of choice in patients with diffuse goitre over 45 years who are not fit for operation, but in other patients it has so far been reserved for recurrent goitres and those not responding to other treatment. It seems likely that ^{131}I will be used more widely in elderly people as there are still no reports of it inducing carcinomatous change in man, although there is probably an increased incidence of leukæmia in patients treated for thyroid carcinoma with very high doses.

Conclusion. Sub-total thyroidectomy after thorough medical preparation is satisfactory for most patients, but the advantages and disadvantages of the possible treatments should be considered for each individual. Usual treatments may be summarised:

Type of toxic goitre	*Under* 45 *years*	*Over* 45 *years*
diffuse	drugs for small, surgery for large, goitres	^{131}I, drugs or surgery
nodular	surgery	surgery
recurrent	^{131}I	^{131}I

The mortality rate of surgical treatment in the best centres is now extremely low, but so is that due to agranulocytosis now that less toxic drugs are available.

Therapeutic Myxœdema has been induced with antithyroid drugs (including ^{131}I) in cases of angina at rest or intractable heart failure. Gross myxœdema is required if the work done by the heart is to be usefully reduced.

GUIDE TO FURTHER READING ON THYROID HORMONES AND ANTITHYROID DRUGS

(*1*) ASTWOOD, E. B., *et al.* (1943). Action of certain sulfonamides and of thiourea upon function of thyroid gland of rat. *Endocrinology*, **32**, 210.

(*2*) PITT-RIVERS, R. (1950). Mode of action of antithyroid compounds. *Physiol. Rev.*, **30**, 194.

(*3*) KIMBALL, O. P. (1928). The efficacy and safety of the prevention of goitre. *J. Amer. med. Ass.*, **91**, 454.

(*4*) Symposium on the pathologic physiology of thyroid diseases. *Amer. J. Med.*, 1956, **20**, 651–744.

(*5*) PITT-RIVERS, R., and TATA, J. R. (1959). The Thyroid Hormones. London: Pergamon Press.

(*6*) WERNER, S. C., editor (1955). The Thyroid. London: Cassell.

Chapter 23

INSULIN AND DIABETES

THE secretion of insulin by the β cells of the islets of Langerhans is probably controlled by the amount of glucose in the blood supplying the pancreas. A raised blood-glucose level stimulates insulin secretion, which reduces the blood glucose to normal levels.

Insulin is a protein and so is ineffective by mouth because it is digested. Although its formula is known it has not been synthesised and purified preparations of animal insulin are used in therapeutics. Fortunately there is no species specificity for insulin.

Metabolic Effects of Insulin

Insulin promotes the uptake and utilisation of glucose from the blood by the tissues. Exactly how it brings this about is not certainly known and there are many hypotheses (*1*, *2*). Insulin deficiency thus results in reduced carbohydrate metabolism and this leads to very many secondary disturbances, which are reversed when insulin is given.

The main effects of insulin are:—

1. **Lowered Blood Sugar,** achieved mainly by increasing the peripheral utilisation of glucose, but partly by promoting the synthesis and storage of glycogen in the liver. When the blood-glucose level falls below the renal threshold (180 mg./100 ml.) glycosuria ceases, as does the accompanying osmotic diuresis of water and electrolytes. Polyuria with dehydration and excessive thirst are thus alleviated. If the blood glucose falls below normal levels appetite is stimulated.

2. **Reduced Metabolism of Fat.** If glucose cannot be burnt to provide energy then fat is burnt instead, so that the presence of adequate amounts of insulin prevents excessive breakdown of fat.

3. **Reduced Ketosis.** Excessive breakdown of fat and protein leads to accumulation of keto-acids which cannot be further metabolised in the absence of normal carbohydrate metabolism. Adequate amounts of insulin restore carbohydrate metabolism and so allow rapid oxidation of the acid end-products of fat metabolism, even if they are present in large amounts, as in diabetic ketosis.

4. **Reduced Gluconeogenesis.** When insulin is deficient large amounts of protein are converted into glucose and the patient becomes wasted.

5. **Tissue Formation** is thus promoted by allowing incorporation of

protein into cells (4 above), by allowing fat deposition (2 above) and by promoting carbohydrate storage as liver glycogen (1 above). This increase in tissue formation is largely responsible for the increase in weight which usually follows insulin administration. Correction of dehydration and increased appetite (1 above) are other factors.

Indications for Insulin Therapy

The main indication is in the treatment of diabetes mellitus. Soluble insulin is sometimes given in small doses (10 I.U. 3 times a day, half an hour before meals) to stimulate appetite and promote an increase in weight, *e.g.* in anorexia nervosa. Insulin shock therapy has been widely used in the treatment of schizophrenia; it is a highly specialised technique requiring very careful control.*

Preparations of Insulin

These are all sterile aqueous solutions or suspensions. Soluble insulin may be given s.c., i.m., or i.v. The long-acting preparations are given only s.c.; given by i.m. injection they would have a different time-course of action and could not easily be self-administered. Dosage is measured in International Units (I.U.).

Soluble insulin is available in a solution containing 20 I.U./ml. (single strength), 40 I.U./ml. (double strength) and 80 I.U./ml. (quadruple strength). The long-acting preparations are only available in strengths of 40 and 80 I.U./ml. More concentrated preparations can be provided to meet rare special cases.

In each individual diabetic it is necessary to find the most suitable insulin preparation by trial and there is a wide variety from which to choose (see p. 377). It should not be difficult to select a suitable form of insulin for the majority of patients, but if none of those in the table is suitable it is possible to get more critical adjustment by mixing semilente and ultralente insulins in proportions different from those in lente insulin (see below) or to add soluble insulin to protamine zinc insulin to obtain more rapid effect. When this latter is done some of the soluble insulin is converted to protamine zinc insulin, so that the early effect of such a mixture is not as great as if the soluble insulin had been given separately. This particular mixture is not stable and should be used at once. It is clear that perfect control of the blood glucose level cannot be obtained by a single daily injection, for insulin requirements fluctuate during the day and single dose regimes are a compromise.

---

* Sargant, W. and Slater, E. (1954). An Introduction to Physical Methods of Treatment in Psychiatry. 3rd Ed. Edinburgh: Livingstone.

THE APPROXIMATE TIME RELATIONSHIPS OF THE CHIEF INSULIN PREPARATIONS, ASSUMING THEY ARE GIVEN S.C.

Type of Insulin	*Onset hours*	*Peak Action hours*	*Duration hours*
soluble	1	2–3	6–8
globin zinc	1–2	6–12	18–24
isophane	1–2	10–20	20–30
zinc suspension, lente	1–2	10–20	20–30
zinc suspension (amorphous), semilente	1–2	9–14	12–16
zinc suspension (crystalline), ultralente	4–6	16–24	24–30
protamine zinc	4–6	16–24	24–48

There is very great individual variation in response.

Soluble Insulin is an aqueous solution of insulin. It is simple to use, being given s.c. 3 times a day, half an hour before meals. There is relatively little risk of hypoglycæmic reaction. If it is known that a meal must be delayed, then the insulin injection can be postponed. The dose can easily be adjusted according to the amount of glycosuria. For these reasons it is often used initially to balance diabetics needing insulin. Soluble insulin is the only satisfactory preparation for the treatment of diabetic ketosis, when it may have to be given in very large amounts both i.v. and i.m. The biggest disadvantage of soluble insulin for long-term use is the need for 3 injections a day, and even then heavy glycosuria is likely before breakfast.

Protamine Zinc Insulin (P.Z.I.) is a depôt preparation, the combination of insulin with protamine and zinc making it less soluble. If enough is given in a single early morning injection to abolish glycosuria throughout the 24 hours, then severe hypoglycæmic reactions tend to occur at night or before breakfast. The dose of protamine zinc insulin may therefore have to be too low to give complete control, and small amounts of soluble insulin are often given in addition, usually before breakfast, but sometimes later in the day as well.

Globin Zinc Insulin is another depôt preparation which is usually given once a day but an occasional diabetic seems to do best on two injections.

Isophane Insulin or N.P.H. (Neutral, Protamine, Hagedorn) insulin is a stable mixture of soluble insulin and protamine zinc insulin with a curve of action similar to that of Insulin Zinc Suspension, B.P. (lente insulin).

Insulin Zinc Suspensions (the lente insulins) (*3*) have more recently been developed in Denmark. Their chief advantages are that they contain no protein other than insulin, so that hypersensitivity reactions are rare, and that a single daily injection can give fairly smooth control of the blood sugar throughout the 24 hours. The speed at which insulin is absorbed from the injection site varies with the particle size.

The *amorphous* insulin zinc suspension (semilente) is rapidly absorbed.

The *crystalline* insulin zinc suspension (ultralente) is not, because the particle size is larger.

Insulin Zinc Suspension, B.P., often referred to as lente insulin, consists of 3 parts of semilente and 7 parts of ultralente insulin.

Over 80% of diabetics needing insulin can be managed satisfactorily on Insulin Zinc Suspension.

Side Effects of Insulin

Unwanted effects of insulin are mainly those of hypoglycæmia. Hypoglycæmia may lead to coma, convulsions and very rarely to death. Because the brain requires glucose as its source of energy, an adequate blood-glucose level is just as essential as an adequate supply of oxygen.

It is usually easier to differentiate hypoglycæmia from severe diabetic ketosis than from other causes of coma, which are as likely in a diabetic as in anyone else. If there is doubt as to the ætiology in a comatose patient it is reasonable to give 50 ml. of 50% glucose i.v., but only after taking blood for a sugar estimation. If hypoglycæmia of short duration is responsible then a rapid improvement is usual, if it is not then that amount of glucose will do no harm.

Other unwanted effects of insulin include atrophy of fat, or development of lipomata, at the injection sites. Generalised hypersensitivity reactions are very rare, but may occur to minute traces of extraneous animal protein in soluble insulin, to protamine or globin in the respective depôt preparations, or even to insulin itself. Therefore change of brand of insulin may prevent the undesirable reactions. Desensitisation is sometimes possible.

Treatment of a Hypoglycæmic Attack

Prevention depends very largely upon the education of diabetic patients taking insulin. In particular, they should never miss meals and must know the early symptoms of an attack. They should carry glucose sweets or lump sugar about with them and should carry a special card identifying them as diabetics. This card should request that if the bearer is found behaving strangely he should be given sugar. Treatment is always to give sugar, either by mouth if the patient can still swallow, or i.v. as 50% glucose (20 to 100 ml.). The response is usually dramatic, but if the patient has been severely hypoglycæmic for some hours or if very large amounts of insulin have been taken, then large amounts of glucose may have to be given by i.v. infusion for several days. Very severe attacks sometimes damage the central nervous system permanently.

Hormones which Tend to Raise the Blood Sugar

These include:—

Adrenaline, which raises the blood sugar by mobilising liver glycogen and does not antagonise the peripheral actions of insulin. Adrenaline was once recommended in the treatment of hypoglycæmia, but endogenous adrenaline is secreted reflexly before symptoms become apparent and glucose provides safer and much more effective therapy. Glycosuria and diabetic symptoms may occur in patients with a phæochromocytoma.

Adrenocortical Steroids, either endogenous or exogenous, antagonise the effects of insulin, although this effect is only slight with the primarily sodium-retaining group; the adrenocortical hormones *increase* gluconeogenesis and reduce glucose uptake and utilisation by the tissues. Patients with Cushing's syndrome thus develop diabetes very readily and are resistant to insulin. Patients with Addison's disease are abnormally sensitive to insulin.

Pituitary Growth Hormone antagonises the actions of insulin at the periphery. Acromegalic patients may develop insulin-resistant diabetes. Conversely patients suffering from hypopituitarism are abnormally sensitive to insulin.

Thyroid Hormone increases the requirements for insulin.

The Treatment of Diabetes Mellitus

All diabetics should keep to a diet if they are to reduce the incidence of the complications of the disease. Some need insulin in addition.

The aim of treatment is to get as close as possible to the ideal of a normal blood sugar throughout the 24 hours. Each diabetic patient should be assessed individually; only an outline of the general principles involved can be given here:—

Education. All diabetics should possess a book* which contains general information about the treatment of the disease and detailed diets. Diabetics should understand that there is good evidence that proper control minimises the risk of serious complication such as blindness. If taking insulin they should know how to give their injections and test their urine. It is important to stress that any infection or other pyrexial illness increases the metabolic rate, which means that they should *increase* their insulin and take enough food or glucose to cover it.

---

* *E.g.* Notes for Diabetics (1956). Diets and instructions given to patients attending the diabetic clinic, University College Hospital. 5th ed. London: Lewis. *or* LAWRENCE, R. D. (1959). Almost All About Diabetes. London: British Medical Assoc.

Diet should be simple. Carbohydrate restriction is essential, but the degree of restriction varies considerably from patient to patient according to their total caloric requirements (100 to 300 G. carbohydrate a day may be needed). An adequate protein intake (75 to 100 G. a day) is essential, and fat intake should not be less than 40 G. a day. Caloric requirements vary from 800 to 4,000 a day, according to the patient's type of work, body size and whether weight increase or reduction is desirable. The way in which the total Calories are distributed through the day varies with the type of insulin taken.

Weight. Many diabetics are obese, and may cease to show glycosuria when their weight is reduced. Elderly fat diabetics form a group whose blood does contain some insulin, but who are resistant to its action; they seldom become ketotic. Younger patients with diabetes are often underweight and need insulin to restore normal weight. The blood of these young diabetics contains no insulin, and they are sensitive to its action; they readily become ketotic.

Insulin. Diabetic ketosis is an absolute indication for insulin and admission to hospital, as is any severe acute illness in a diabetic. Other indications are weight loss in a thin diabetic or inadequate control of the blood sugar and glycosuria with diet alone. If it is decided that insulin as well as diet is needed in a mild case then it is reasonable to start straight away with a morning injection of Insulin Zinc Suspension, B.P. (say 20 I.U. daily). However, more severe cases should be balanced with 3 injections of soluble insulin a day, preferably in hospital, and changed to a longer-acting preparation later if possible. When this is done the initial dose of the long-acting preparation should not exceed two-thirds of the previous daily total. If the daily dose of any long-acting or depot insulin exceeds 40 I.U., nocturnal or early morning hypoglycæmia is liable to occur. If much larger doses are needed it may be better to give some as soluble insulin before meals.

Muscular activity increases carbohydrate utilisation, so that hypoglycæmia is likely if a well-stabilised patient changes suddenly from an inactive hospital existence to a vigorous life outside. If this is likely to happen the dose of insulin should be reduced by up to one-third and then readjusted according to need.

Diabetic Complications may be largely prevented by meticulous control of the blood sugar. The care of diabetics undergoing surgery is specialised. Details can be found in Appendix C.

In pregnancy (5) insulin requirements are liable to increase steadily after the third month. During labour soluble insulin should be given 4-hourly with plenty of glucose orally. Substantially less insulin is likely to be needed immediately after delivery, when at least one injection of insulin should be omitted or hypoglycæmia may occur. Insulin requirements may increase again during lactation. Blood glucose estimations are necessary during the latter part of pregnancy, for glycosuria is not then a reliable guide as the renal threshold for glucose falls, so that glycosuria may occur in the presence of a normal blood glucose. Heavy loss of glucose may occur as a result of this and complicate the management of the patient. Some physicians advocate the admission to hospital of all diabetics after the 32nd week of pregnancy for careful control of the diabetes until after delivery.

Tuberculosis is serious in a diabetic and it is important to diagnose and treat it early. Peripheral vascular disease and its consequences such as intermittent claudication, ulcers and gangrene, are very common among diabetics. Treatment is the same as in non-diabetics. Cramps in the legs are often helped by quinine (600 mg. of the bisulphate, nightly). Peripheral neuritis may occasionally be improved by aneurine.

Diabetic Ketosis*

Definition and Nature. Diabetic ketosis is an acute acidosis caused by a disturbance of carbohydrate metabolism due to a relative or an absolute lack of insulin. It is always complicated by cellular and extracellular dehydration, and by depletion of body sodium, potassium and water, due mainly to renal losses, and to lack of replacement because of vomiting. The acidosis results from an accumulation of keto-acids and is partly compensated by renal mechanisms and by hyperventilation. Heavy glycosuria promotes an osmotic diuresis and is an important factor in causing dehydration. In severe cases dehydration leads to peripheral circulatory failure and extrarenal uræmia.

Causes. The common precipitating causes are an acute infection, usually respiratory, renal or gastro-intestinal; omission of insulin, or lack of insulin in an untreated diabetic; less commonly, coronary thrombosis, gangrene, cerebral vascular accident or a surgical emergency. It is therefore largely preventable.

Treatment. The aim is to correct simultaneously:—

1. The abnormality of carbohydrate metabolism (by giving insulin),
2. dehydration (by i.v. infusion),
3. acidosis (by giving sodium lactate and bicarbonate),
4. sodium and potassium depletion (by the i.v. infusion),
5. infection (by giving appropriate antimicrobial)

and any other complication is treated appropriately.

Details of the treatment of diabetic ketosis may vary, but the principles are the same.* Adequate amounts of insulin are urgently needed or the patient's condition will steadily deteriorate.

---

* This account is based on that written by Dr. A. G. Spencer for the University College Hospital Handbook, 1959.

Blood is taken (for glucose, electrolyte and urea estimations) through the same needle as is used to set up an i.v. infusion of saline-lactate (see below). Soluble insulin is given immediately:—

Severe Cases (coma, infection):
50 to 100 I.U. i.v.
plus: 200 I.U. i.m.

Moderate Case:
25 I.U. i.v.
plus: 50 to 100 I.U. i.m.

Mild Case:
50 I.U. i.m.

(Insulin should *not* be given s.c. when treating severe ketosis as it may not be absorbed because of peripheral circulatory failure.) Subsequent i.m. injections of soluble insulin are given at intervals of 2 to 6 hours according to the clinical response, and urine and blood sugar tests. These doses can usually be smaller, but occasionally very large amounts of insulin are required, such as 5,000 I.U. in 24 hours. Long-acting insulins should not be used. Fluids by i.v. infusion are essential in all but the very mildest cases. In severe cases 1 litre of saline-lactate† is given in 30 minutes, followed by another over 2 hours. There is no point in giving solutions containing glucose *early* in treatment as they increase glycosuria and fluid loss and make blood sugar estimations useless. After 2 to 4 hours of treatment, or later, there may be a sharp fall in the serum potassium as it is taken up by the cells. This may cause gastric dilatation and even sudden cardiac arrest. To avoid this the saline-lactate solution is followed by a glucose electrolyte solution‡ which will help maintain the serum potassium level. Provided the urine volume is more than 100 ml. an hour, 3 litres of glucose-electrolyte solution should be given by infusion at a rate not faster than a litre over 4 hours. If the urine volume is less than 100 ml. an hour, 5% glucose with 0·45% sodium chloride solution should be given. In the elderly, and if there is evidence of heart failure, of a recent coronary thrombosis or of renal disease, i.v. fluids should be given more slowly. If the blood pressure is less than 110/60 mm. Hg. after 2 hours treatment, or if there is other evidence of circulatory failure, 500 ml. of blood or plasma should be given over 2 hours. Injection of sympathomimetic vasoconstrictor drugs may be used as a temporary measure if the blood pressure is very low, but should be avoided whenever possible. No fluids or solids should be given by mouth for 12 to 24 hours if there has been any vomiting in the previous 24 hours. Stomach washout is seldom required if oral fluids are withheld. If vomiting or nausea is persistent the stomach should be washed out with 2% sodium bicarbonate solution to remove the sticky mucus which accumulates.

---

* Nabarro, J. D. N., Spencer, A. G. and Stowers, J. M. (1952). Lancet, i, 983.

† Many solutions differing slightly in composition are used. Those in use at University College Hospital are (in mEq. l.):

saline-lactate: sodium 130, chloride 100, lactate 30;

‡ glucose-electrolyte: sodium [illegible], potassium [illegible], magnesium [illegible], chloride [illegible], phosphate 10, in 5% glucose.

Any infection should be treated with full doses of the appropriate drug. Penicillin, to protect against hypostatic pneumonia, and a sulphonamide to prevent urinary infection due to catheterisation, are often given (p. 28).

Hypoglycæmia is liable to occur after 12 to 24 hours of treatment. To avoid this, as soon as the glycosuria is about 1% or less, or the blood sugar 300 mg./100 ml. or less, insulin is omitted for the next 4 hours or until glycosuria exceeds 1%.

Progress Chart. In every case it is essential to keep an up-to-the-minute chart of the patient's condition, pulse, blood pressure, urine volume and tests, blood chemistry, insulin and antimicrobial dosage and a record of the i.v. and oral fluids given.

Subsequent Course. After 12 to 24 hours treatment the severe case of ketosis should be fit to treat in the way recommended for the mild case. After 24 to 48 hours he may be given a light 1,000 Calorie diabetic diet and soluble insulin 3 times a day, adjusted according to the urine tests. In a few days the patient should return to his former régime, but will probably require more insulin during the next 2 weeks. He should be warned that his insulin requirements will probably drop and to adjust the insulin dose according to the results of urine sugar tests.

Mild Diabetic Ketosis. If the patient is fully conscious and there has been no nausea or vomiting for at least 12 hours, parenteral therapy is unnecessary. It is reasonable to give soluble insulin i.m., 50 I.U., every 4 hours and 1 litre of 5% glucose in 0·45% sodium chloride solution by mouth (lemon flavoured).

Oral Hypoglycæmic Drugs (*6*)

Since 1942 it has been known that sulphonylurea compounds could produce hypoglycæmia in animals, provided that the pancreas was intact. It was not until 1955 that clinical trials took place and it was found that some of the compounds were effective in controlling certain diabetics. The drugs in use include carbutamide, tolbutamide and chlorpropamide. These substances appear to act by increasing insulin secretion by the pancreas. They are thus only useful in patients who have some active insulin-secreting cells, and are not recommended for the "insulin deficient" diabetic, a group which includes nearly all diabetics diagnosed before

40 years of age. The older obese mild diabetic is more likely to respond, but if obesity is marked the diabetes can commonly be controlled by diet alone, so that only those of average or below-average weight need be considered as possible subjects for these drugs. It is impossible to be dogmatic about who should take the oral hypoglycæmic agents. Perhaps only those who are unwilling, or unable, to give themselves injections of insulin should be exposed to their not insignificant toxicity.

Unwanted effects of tolbutamide, which is perhaps the least toxic of this group, include weakness, paræsthesiæ, tinnitus, headache and gastro-intestinal upset. Rashes and leukopenia may occur. Since tolbutamide has been shown to interfere with some liver enzymes it should probably not be given in the presence of hepatic disease. Changeover from insulin to tolbutamide in a case of moderate severity should be gradual. 3 G. total should be given on the first day in three doses, 2 G. total on the second day and 1 G. on the third day, whether or not the patient is taking insulin. Maintenance dosage is likely to be about 0·5 to 1 G. a day in one or two doses. Mild cases may begin on 1 G. a day without the priming doses recommended above. If, when changing over from insulin, ketonuria occurs, the patient should instantly return to insulin.

Another drug chemically unrelated to tolbutamide, phenformin (phenylethyldiguanide, DBI) has been introduced. Its mode of action differs from that of the sulphonylureas and it does have some effect in insulin-deficient diabetes if used in conjunction with insulin. Ketosis with a *low* blood sugar can occur with this drug. It is clear that a great deal more experience of this and the sulphonylureas will be needed before their place in therapeutics can be evaluated. There is likely to be proliferation of drugs in this group.

GUIDE TO FURTHER READING ON INSULIN AND DIABETES

(1) Stadie, W. C. (1954). Current concepts of the action of insulin. *Physiol. Rev.*, **34**, 52.

(2) Ross, E. J. (1956). The "permeability" hypothesis of the action of insulin. *Medicine* (*Baltimore*), **35**, 355.

(3) Lancaster, W. M., and Murray, I. (1958). Further experience with the "Lente" insulins. *Brit. med. J.*, (*i*), 1331.

(4) Symposium on recent advances in diabetes (1952). *J. Amer. med. Ass.*, **150**, 959.

(5) Peel, J. H. (1959). Diabetes mellitus associated with pregnancy. *In* British Obstetric and Gynaecological Practice. Ed. E. Holland. London: Heinemann.

(6) Editorial (1957). Tolbutamide in diabetes. *Brit. med. J.*, (*ii*), 345.

(7) Joslin, E. P., Root, H. F., White, P., and Marble, A. (1959). The Treatment of Diabetes Mellitus. 10th ed. London: Kimpton.

(8) Insulin. *Brit. med. Bull.*, 1960, **16**, part 3.

Chapter 24

IRON, CYANOCOBALAMIN, FOLIC ACID

IRON

Iron, which was the metal symbolising strength in magical systems, used to be given to people suffering from weakness, and no doubt some were benefitted, some psychologically (placebo reactors) and others because they had anæmia. The rational use of iron could not begin until both the presence of iron in the "colouring matter" of the blood and the "defective nature of the colouring matter" in anæmia were recognised. Early in the 19th century Dr. Pierre Blaud recognised many of the important principles of iron therapy. He said that iron should be given in inorganic form, that small doses should be given at first and increased gradually to relatively high doses. He introduced his Pills, containing ferrous carbonate and sulphate. Unfortunately a number of eminent physicians towards the end of the last century considered, for purely theoretical reasons, that inorganic iron could not be absorbed, so that many expensive and relatively ineffective organic iron preparations were developed. Modern experiments have re-established the soundness of Blaud's ideas.

Iron Absorption (*1*)

Iron absorption takes place mainly in the acid medium of the upper part of the small intestine. Iron metabolism is unusual in that there is a "mucosal-block" so that however much iron is present in the intestine (within ordinary limits) only the amount that is needed is absorbed. The details are not fully understood, but it seems that when iron enters the mucosal cells it combines with a protein, apoferritin, to form ferritin. When the apoferritin is all converted to ferritin no more iron can enter the cells, "mucosal-block" has occurred. The ferritin in the mucosal cells is in equilibrium with the iron transporting protein (transferrin) in the plasma. This in turn is in equilibrium with the ferritin and hæmosiderin, especially in the liver and spleen, which make up the iron stores of the body. Thus depletion of the iron store (as in pregnancy, or after a hæmorrhage) is made good by increased absorption through the intestinal mucosa. Obviously this mechanism can prevent iron deficiency only when there is sufficient available iron in the intestine. The normal mucosal-block is overwhelmed in acute iron poisoning and a deficiency in the block leads to hæmochromatosis (p. 390).

Iron can only be absorbed in soluble ferrous form, ferric iron has first to be reduced. A powerful reducing agent, such as ascorbic acid in large doses (200 mg. 3 times daily) greatly increases the absorption of iron from food or medicine, but small doses of reducing agents are useless.

Abnormalities of the gastro-intestinal tract may interfere with either the absorption of iron, as in the malabsorption syndromes and cœliac disease, or possibly with the conversion of iron into a soluble and reduced form. The formation of insoluble iron salts (such as phosphate and phytate) in the alkaline medium of most of the small intestine probably explains why much of the iron taken by mouth is not absorbed, even in severe iron deficiency.

It used to be thought that many forms of iron could not be utilised at all. However, using a radio-active isotope of iron (^{59}Fe) it has now been shown that a varying proportion of the iron in almost all iron compounds, ranging from steel filings to hæmoglobin, can be converted into a soluble ferrous form and absorbed. Vegetables grown in nutrient solutions of ^{59}Fe have been fed to both normal and iron deficient volunteers, by which means the proportion of iron absorbed from various foods as well as therapeutic preparations can be measured using a scintillation counter (5). It has been found that normally about 10% of the iron in the diet, or in iron supplements, is absorbed. In iron deficiency this proportion is greatly increased, sometimes to as much as 60%.

Iron Requirements

60 to 70% of the 5 grams of iron in the body is in hæmoglobin, about 20% is stored as ferritin and hæmosiderin and the remainder is combined with various proteins in blood plasma and tissue cells (*e.g.* myoglobin, respiratory enzymes).

An adult man loses only about 1 mg. of iron a day from cells desquamated from skin and gut, from sweat and in the urine. However, in women this is increased to an average of about 2 mg. a day by the losses in menstruation; in pregnancy more is diverted to the fœtus. At first sight the daily 15 mg. of iron in the average Western diet would appear to allow an adequate margin, but since only about 1·5 to 2 mg. of this are available for absorption, the iron balance of babies, children and women before the menopause is precarious.

Iron Deficiency. The symptoms and signs of iron deficiency are mostly due to anæmia, which is usually microcytic and hypochromic, and is characterised by a low Mean Corpuscular Hæmoglobin Concentration (normal M.C.H.C. is 34 G./100 G. erythrocytes). The sore tongue, atrophic skin and nail changes found in iron deficiency anæmia are possibly due to a reduction in the amount of iron-containing enzymes which are necessary for renewal of epithelial cells.

Iron Therapy

This is only indicated for the prevention or cure of iron deficiency. 25 mg. of iron per day must be available to the bone marrow if an iron deficiency anæmia is to respond with a rise of 1% of hæmoglobin per day. This must be doubled if the iron stores are also to be quickly replenished and a common cause of relapse is to give only enough to raise the hæmoglobin without filling the stores. It may be impossible to build up depleted iron stores by oral administration of iron because iron absorption reverts to normal once the anæmia is corrected. Although this cannot be regarded as finally proved it has been used as an argument for the more frequent use of iron injections.

With oral preparations it is reasonable to assume that about 30% of the iron will be absorbed and to give about 150 mg. of elemental iron daily. If it is necessary to replace an iron deficiency parenterally, a total of about 50 mg. of iron for each per cent that the hæmoglobin is deficient is required. It is illogical to give iron in hæmolytic anæmias, as the iron from the hæmolysed cells remains in the body.

Iron therapy is needed:—

1. In iron deficiency due to chronic blood loss.

2. In pregnancy. The fœtus takes 300 to 400 mg. of iron from the mother even if she is iron deficient, but the iron stores of a baby born to such a mother will be abnormally low. Dietary iron is seldom adequate and iron should be given to all expectant mothers, who should be warned not to let children get at the tablets, which are usually attractively coloured.

3. In various abnormalities of the gastro-intestinal tract where the proportion of dietary iron absorbed may be reduced (*e.g.* in malabsorption syndromes generally).

4. In premature babies, since they are born with low iron stores, and in babies weaned late. There is very little iron in human milk and even less in cow's milk.

5. During the treatment of severe pernicious anæmia with cyanocobalamin, as the iron stores occasionally become exhausted.

Oral Iron Preparations

There is an enormous variety of official and proprietary iron preparations. For each milligram of elemental iron taken by mouth, ferrous sulphate is as effective and no more toxic than more expensive preparations (*6*). Solutions of iron salts are seldom used as they stain the teeth. It is particularly important to avoid initial overdosage with iron as the resulting symptoms may cause the patient to abandon iron therapy. A small dose is given at first and increased after a few days. If given on a full stomach iron causes less toxic effects, but less is absorbed than if it is given between meals. Commonly used preparations include:—

Ferrous Sulphate Tablets, B.P. The dose is 200 to 800 mg. daily. Each 200 mg. tablet contains 40 mg. of elemental iron.

Ferrous Gluconate Tablets, B.P. The dose is 300 to 1,200 mg. daily. Each 300 mg. tablet contains 35 mg. of elemental iron.

Ferrous Carbonate Tablets (Blaud's Pill) are obsolete because they are relatively insoluble and may deteriorate on keeping.

The following mixtures are preferred to tablets by an occasional patient; they are available in less concentrated, flavoured solutions for infants.

Ferrous Sulphate Mixture, B.N.F. 15 ml. contains 60 mg. of elemental iron. The dose is 15 to 60 ml. daily.

Ferric Ammonium Citrate Mixture, B.P.C. 15 ml. contains 350 mg. of elemental iron. The dose is 15 to 60 ml. daily, this large amount of iron is necessary because it is in the ferric form. It would seem particularly desirable to give ascorbic acid with this preparation, although it has been used without for many years.

Colloidal Ferric Hydroxide (Colliron) can be used. It is said to be relatively free from gastric side-effects.

Parenteral Iron Preparations

Parenteral administration may be required if iron cannot be absorbed from the intestine, if a quick and certain response is essential in a severe iron deficiency anæmia, as in late pregnancy or if, as sometimes happens for no known reason, oral iron therapy fails, or the patient cannot be relied on to take a sufficient oral dose regularly. The approximate total requirement can be calculated from the hæmoglobin level (p. 387). The ionised salts of iron are extremely powerful protein precipitants and cannot be used parenterally.

Saccharated Iron Oxide (Ferrivenin) is given by slow intravenous injection. 1 ml. of the usual solution contains 20 mg. of elemental iron. The initial dose is 1 to 2 ml. given in 2 minutes, followed, if no reaction has occurred, on the next and subsequent days by 5 ml. in 5 minutes until the required amount of iron has been given. It is irritant and causes pain and sometimes tissue necrosis if injected outside a vein. General toxic reactions include flushing, dizziness, pallor, fall of blood pressure, tachycardia, dyspnœa, cyanosis, pain in the chest, vomiting, generalised aches and pains, fever and rigors. They may occur during the injection, or up to a few hours after it. At least 5% of patients are liable to some or all of the toxic reactions, but these are undoubtedly minimised by giving the injection slowly.

Iron dextran Complex (Imferon) has been widely used as the least toxic preparation of iron for parenteral use. After iron-dextran complex had been in use for some years it was found that huge doses repeatedly injected into the same site in rats caused local sarcoma. This raises the question of the relevance of animal toxicity tests to clinical practice.* It is reasonable to agree with the discoverer of this highly undesirable toxic effect that "The clinical significance of these observations cannot be assessed pending elaborate study of the many factors involved."† It is not possible, however, to avoid considering whether the clinical use of such a substance should continue. A reasonable view would perhaps be that iron-dextran complex should only be used i.m. where there is special reason to do so, where i.v. injections of saccharated iron oxide are toxic or impracticable for any reason. The evidence available so far does not warrant complete condemnation of this useful preparation. Iron-dextran complex should certainly not be used lightheartedly, but it may also be remembered that under appropriate circumstances glucose has been shown to be carcinogenic so that the interpretation of such experimental findings is fraught with difficulty.‡

Iron-dextran complex is given by deep i.m. injection. It stains the skin, but this can be minimised by inserting the needle through the skin and then moving the skin and subcutaneous tissue over the muscle before entering it so that the needle track becomes Z-shaped when the needle is withdrawn. 1 ml. of the usual solution contains 50 mg. of elemental iron. The initial dose is 2 ml., which is followed by either 2 ml. daily or 5 ml. twice a week until the total amount of iron required has been given. The injections are usually painful and general reactions like those to saccharated iron oxide sometimes occur but are less frequent.

Toxic Effects of Iron

High doses of iron salts by mouth can cause severe gastro-intestinal irritation and even necrosis of the mucous membrane, with vomiting, hæmatemesis and diarrhœa. The mucosal-block is overwhelmed, and shock with cardiovascular collapse occurs. Autopsy has shown severe damage to brain and liver. Tablets of most iron preparations are attractive to children because they are senselessly highly coloured and sugar-coated. Death may occur if an infant swallows a quantity of these "sweets" whose danger is not sufficiently recognised.

" . . . a girl aged 19 months was found vomiting after taking 15 or 16 ferrous sulphate tablets. She was taken to hospital and there given salt and water and she vomited again. The mother was told that there were no beds available and she was sent to another hospital. Here she was told that the tablets were not poisonous and would do the child no harm. The child was retching now but not vomiting and the mother was told to take her home and give her plenty of milk to drink. The mother was not satisfied and took the child to another doctor on the way home. He told her to give the child orange juice to drink and she would be all right. The mother then took the child home, put her in her cot, and went to make some orange juice. When she returned the child was dead . . . about four hours after the child had taken the tablets."* Treatment is urgent but not specific (p. 429). Dimercaprol is useless and may even be harmful.

---

* Walpole, A. L., and Spinks, A. (1958). Evaluation of Drug Toxicity. London: Churchill.

† Richmond, H. G. (1959). *Brit. med. J.*, (*i*), 947.

‡ See also, Editorial (1960). *Brit. med. J.*, (*i*), 788. Golberg, L. (1960). *Brit. med. J.*, (*i*), 958.

No doubt this topic will be debated for a long time to come.

Ordinary doses of iron preparations sometimes, and slight overdoses very frequently, cause milder gastro-intestinal disturbances. These are minimised if the initial dose is small and then cautiously increased. Nausea, abdominal pain, and either constipation or diarrhœa, may occur. Gossip leads expectant mothers to anticipate being upset by iron tablets, and one blind controlled trial has shown that nausea, heartburn, flushes, constipation and diarrhœa were just as common in the control group receiving dummy tablets as in the group taking adequate amounts of iron (7). The motions are coloured black by iron but this does not interfere with the benzidine test for occult blood.

Chelated Iron Compounds that are absorbed more slowly than the other preparations have recently been prepared. They are therefore less dangerous to children and possibly cause fewer toxic effects. They are still being evaluated.

Iron Overload. The body is unable to excrete any excess of iron and so if the mucosal-block does not function, iron steadily accumulates in the body and hæmochromatosis eventually results. Grossly excessive parenteral iron therapy, or a hundred or more blood transfusions, can also lead to hæmochromatosis. Oral iron therapy has never been reported to cause hæmochromatosis.

Deficiencies of Other Metals

Copper, cobalt, molybdenum and manganese deficiencies have all been postulated as rare causes of otherwise unexplained anæmias. The evidence is seldom convincing and they have no place in therapeutics at present. The use of cobalt in anæmia has occasionally been followed by goitre and nephritis.

---

* SPENCER, I. O. B. (1951). *Brit. med. J.*, (ii), 1112.

EXTRINSIC AND INTRINSIC FACTORS IN PERNICIOUS ANÆMIA

In 1925 Castle performed classical experiments demonstrating that two factors were required to cure pernicious anæmia. He showed that beef muscle and normal human gastric juice were ineffective when given separately by mouth, but that when they were given *together* a good reticulocyte response was obtained. "Consequently it was assumed that some unknown but essential interaction between beef muscle as an extrinsic (food) factor and normal human gastric juice as an intrinsic factor appeared to be required for the restoration of normal hæmatopoiesis in the patient with pernicious anæmia" (*2*). During the succeeding 20 years many unsuccessful attempts were made to isolate both the extrinsic and intrinsic factors from various sources. Soon after crystalline cyanocobalamin (vitamin B_{12}) was isolated in 1948 it became generally accepted as the extrinsic factor. However, the intrinsic factor has eluded isolation although relatively crude preparations from animal stomachs have been used in therapeutics.

Recently Castle's results have been re-interpreted and it has been tentatively suggested that cyanocobalamin is normally absorbed as a peptide, that in diet it is combined with protein, and that normal gastric juice partially hydrolyses this, to liberate the peptide.* Thus the extrinsic factor becomes cyanocobalamin in combination with protein and the intrinsic factor a proteolytic enzyme which hydrolyses this to the peptide. Proof of this hypothesis is lacking and the cyanocobalamin peptide preparations that have been tried in the therapy of pernicious anæmia have not so far been successful.

CYANOCOBALAMIN (VITAMIN B_{12})

Pure crystalline vitamin B_{12} was prepared from liver simultaneously but independently in the U.S.A. and in England in 1948, 22 years after Minot and Murphy first demonstrated the effectiveness of oral liver therapy in pernicious anæmia (*4*). The delay was mainly due to the great difficulties of assay of the vitamin. Assay of different fractions is obviously essential during any purification procedure, and for many years the production of a reticulocyte response in patients with pernicious anæmia was the only method. Research has been greatly helped by the discovery of a microorganism requiring vitamin B_{12} as a growth factor, and this has been used to develop a relatively simple microbiological assay. Vitamin B_{12} was soon shown to contain cobalt and a cyanide radicle and so was given the chemical

* HEATHCOTE, J. G., and MOONEY, F. S. (1958). *Lancet*, (*i*), 982.

name cyanocobalamin, which is now the official name. Its structural formula has been elucidated by crystallographic analysis. Cyanocobalamin is now obtained from cultures of streptomyces.

Function of Cyanocobalamin

A deficiency of cyanocobalamin in the body leads to:—

1. A megaloblastic anæmia (Addisonian, or pernicious, anæmia).
2. Characteristic changes in the brain, spinal cord and peripheral nerves (sub-acute combined degeneration).
3. Abnormalities of epithelial tissue, particularly of the alimentary tract (*e.g.* sore tongue).

The exact ways in which these are brought about are not known, but it seems that synthesis of desoxyribosenucleic acid(DNA) is interfered with at a later stage than in deficiency of folic acid. If cells are to divide the amount of DNA present has to be doubled and it is possible that megaloblasts may be cells unable to synthesise enough DNA for cell division to proceed. Prevention of sufficiently rapid cell division could account for 1 and 3 above, but not for 2.

Requirements of cyanocobalamin are about 0·001 mg. daily. Several years' supply are normally stored throughout the body; in the liver the half-life of cyanocobalamin is about a year. Absorption takes place mainly in the ileum. Animals are unable to synthesise cyanocobalamin and so are directly or indirectly dependent upon micro-organisms for it. Man gets most of his cyanocobalamin from meat; organisms in the human colon synthesise it but it is not absorbed from this part of the intestine. Cyanocobalamin does not occur in plants.

Indications for Cyanocobalamin

These are the prevention and cure of conditions due to its deficiency:—

Pernicious (Addisonian) Anæmia is probably due to a genetically determined defect in the gastric mucosa which is unable to produce the intrinsic factor. A histamine-fast achlorhydria is invariably present. Despite its name, the prognosis of a patient with uncomplicated pernicious anæmia, properly treated, is hardly different from that of the rest of the population. The neurological complications, particularly spasticity, are often permanent, although there may be considerable improvement under treatment. Total removal of the stomach, or atrophy of the mucous membrane in a small post-gastrectomy remnant may, after several years, lead to a similar anæmia.

In the Syndromes Due to the Presence of a Blind-loop of Intestine, a megaloblastic anæmia responding to parenteral cyanocobalamin sometimes occurs. It is possibly due to deprivation of cyanocobalamin by the abnormal intestinal flora. The megaloblastic anæmia in the majority of malabsorption syndromes is due to folic acid deficiency.

Fish Tape-worms high in the alimentary tract are a rare cause of cyanocobalamin deficiency in Scandinavia. Apparently the worm takes up all the cyanocobalamin before the host gets a chance to absorb it.

Dietary Deficiency of cyanocobalamin is very rare in Western countries except among the Vegans, who are a sect of particularly uncompromising vegetarians. In countries where people cannot afford to eat meat, cyanocobalamin deficiency may play some part in the common nutritional megaloblastic anæmia.

Cyanocobalamin has been tried empirically, sometimes in enormous doses, without striking success, in a variety of neurological conditions. In some types of peripheral neuritis, especially the diabetic, it has been thought to give benefit, but controlled trials are lacking.

Preparations and Dosage of Cyanocobalamin

Cyanocobalamin is usually given by i.m. injection. The initial dose in cyanocobalamin deficiency anæmias, including uncomplicated pernicious anæmia, is 100 to 250 micrograms on alternate days for a week, followed by 100 to 250 micrograms weekly until the blood is normal. The stimulation of hæmoglobin synthesis may deplete the iron stores and extra iron may be needed. Failure to respond implies inaccurate diagnosis, or the presence of other additional disease such as carcinoma, myxœdema or chronic infection. If neurological complications have occurred the dosage can reasonably be doubled, but some would give all cases milligram doses initially. Treatment of pernicious anæmia must be life-long and this must be impressed upon the patient; the usual maintenance dose is 100 to 250 micrograms every 2 or 3 weeks. Hæmoglobin estimations are necessary at least every 6 months to check that enough is being given. If milligram doses of cyanocobalamin are given orally, enough often crosses the mucous membrane, but this is unreliable as well as wasteful. Cyanocobalamin is effective when given as a snuff, or in an aerosol, in doses not much larger than by injection.

Radio-active cyanocobalamin labelled with isotopes of cobalt has greatly assisted the study of cyanocobalamin absorption.

Toxic Effects of cyanocobalamin do not occur, but its use as a "tonic" is an abuse of a powerful remedy and may make the diagnosis of pernicious anæmia almost impossible, which is a matter of great importance in a disease requiring life-long therapy.

Intrinsic Factor

Intrinsic factor is available for oral use in the form of dried preparations of animal stomach, but they are obsolete because they are both unpleasant to take and unreliable.

Liver Extracts

Liver extracts for injection are now obsolete for the treatment of pernicious anæmia because they contain sometimes variable and always small amounts of cyanocobalamin; they are also bulky, painful to inject and they sometimes cause allergic reactions. Some consider that they still have a place in the treatment of the multiple deficiencies in nutritional macrocytic anæmias.

FOLIC ACID (PTEROYLGLUTAMIC ACID) (*3*)

Folic acid was so named because it was discovered as a bacterial growth factor present in spinach leaves (folium = a leaf). It is one of the B group of vitamins and was soon shown to be the same substance as that present in yeast and liver which cured a nutritional macrocytic anæmia in Indian women, a similar experimental anæmia in monkeys, an anæmia and growth failure in chicks, and was a growth factor for a variety of micro-organisms.

Functions of Folic Acid

Folic acid is converted into its formyl derivative, folinic acid (citrovorum factor), in the body and this is the active form. Ascorbic acid is necessary for the conversion and the anæmia of scurvy although usually normoblastic may be megaloblastic due to folinic acid deficiency. A deficiency of folic acid leads to a megaloblastic anæmia, probably because in some unknown way it is necessary for the production of the purines and pyrimidines which are essential precursors of desoxyribosenucleic acid (DNA). It acts at an earlier stage in the synthesis than does cyanocobalamin. Folic acid antagonists are sometimes used in treatment of certain leukæmias (p. 413).

Occurrence and Requirements of Folic Acid

Folic acid is widely distributed, especially in green vegetables, yeast and liver. It is present in food in a conjugated form. Many body tissues contain an enzyme which releases the folic acid from the conjugate. Requirements of folic acid are not known because a variable amount is synthesised by bacteria in the intestine and absorbed. It is normally completely absorbed from the intestine, but little is stored in the body.

Indications for Folic Acid

These are the prevention and cure of the megaloblastic anæmia provoked by its deficiency:—

Dietary Deficiency. There is enough folic acid in an ordinary Western diet for normal people, but its deficiency plays some part in the complex nutritional macrocytic anæmias which are common in the underdeveloped areas of the world. A rare megaloblastic anæmia of infancy has been caused by dietary deficiency of folic acid which was absent from certain brands of dried milk.

In Malabsorption Syndromes, particularly steatorrhœa and sprue, poor absorption of folic acid often leads to a megaloblastic anæmia. A folic acid absorption test has been devised as an aid to the diagnosis of steatorrhœa but is not widely used because microbiological assay is necessary to estimate the folic acid.

The Megaloblastic Anæmia of Pregnancy usually responds to folic acid. After delivery the anæmia remits spontaneously and its ætiology remains uncertain, but seems to be due to a discrepancy between the large demands of the fœtus and the amount of folic acid taken in the diet.

Anticonvulsant Drugs, particularly phenytoin, occasionally cause a macrocytic anæmia which responds to folic acid. Folic acid and some anticonvulsants are somewhat similar chemically and it seems possible that their metabolites may compete in some enzyme system to provoke a folic acid deficiency.

Preparations and Dosage of Folic Acid

Synthetic folic acid is available in tablets; 10 to 30 mg. daily may be required. The sodium salt is available in solutions for injection and it is reasonable to start treatment of a severe deficiency by injection. After the first few doses oral supplements are adequate even in the malabsorption syndromes. There is no advantage in giving folinic instead of folic acid, except in the treatment of the toxic effects of folic acid antagonists.

Unwanted Effects of Folic Acid

Toxic effects have not been reported.

In Pernicious Anæmia folic acid is incomplete therapy and must not be used because, although it will improve the anæmia so that diagnosis may be impossible, it does not prevent subacute combined degeneration of the nervous system. A patient with pernicious anæmia who has been given folic acid is in a dangerous situation.

Blunderbuss Anti-anæmic Preparations

There are now specific remedies for many anæmias. "Nevertheless . . . many expensive preparations containing iron, vitamins, liver and stomach extracts, yeast, copper, vitamin B_{12}, folic acid, and often other substances, are on the market and recommended by their manufacturers to the doctor for the treatment of his anæmic patients. These polypharmaceutical remedies rarely contain enough of any constituent to deal effectively with any form of anæmia. . . . Anæmic patients still commonly receive some form of treatment with these blunderbuss preparations before their blood has been examined for the purpose of determining the type of anæmia and the appropriate treatment. Then, when the patient does not fully respond to the remedy given, subsequent blood and marrow examinations may fail to give a clear-cut diagnosis. This difficulty is noticed most often in pernicious anæmia—which is still a fatal condition if not properly treated—since the bone marrow rapidly loses its megaloblastic character even after inadequate anti-anæmic treatment, though this does not necessarily lead to a remission of the anæmic state . . . the danger is more serious, because many of the blunderbuss anti-anæmic preparations contain folic acid, though this is not always recognised by those who prescribe them . . . folic acid induces peripheral neuritis and spinal cord degeneration in patients with pernicious anæmia who had previously showed no signs of such complications, or else makes worse an early peripheral neuritis."*

The following case history shows what can happen:—

An anæmic patient was given a proprietary preparation of iron, which was later found also to contain aneurine, extract of raw liver and folic acid. " . . . her general condition improved greatly. Her appetite returned to normal and her weight increased but the stiffness of her legs began to worsen rapidly . . . she fell and was admitted to hospital for treatment of an infected hæmatoma. After 10 days in bed she was found to be unable to rise or walk . . . the patient was found to have a spastic paraplegia with great muscular weakness, bilateral extensor plantar responses and complete loss of posterior column sensation in both legs. . . . Histamine-fast achlorhydria was demonstrated."† There was a moderate macrocytic anæmia. A diagnosis of subacute combined degeneration of the cord was made and the patient fortunately responded well to vitamin B_{12}. This mishap need never have occurred however.

---

* Editorial (1954). *Brit. med. J.*, (*i*), 573.

† LOWTHER, C. P. (1954). *Brit. med. J.*, (*i*), 564

GUIDE TO FURTHER READING ON IRON, CYANOCOBALAMIN AND FOLIC ACID

(1) CALLENDER, S. T. (1959). Iron absorption. *Brit. med. Bull.*, **15**, 5.
(2) CASTLE, W. B. (1953). Development of knowledge concerning the gastric intrinsic factor and its relation to pernicious anæmia. *New Engl. J. Med.*, **249**, 603.
(3) GIRDWOOD, R. H. (1959). The role of folic acid in the blood disorders. *Brit. med. Bull.*, **15**, 14.

(4) Smith, E. L. (1949). Crystalline anti-pernicious-anæmia factor. *Brit. med. J.*, (*ii*), 1367.

(5) Moore, C. V., and Dubach, R. (1956). Metabolism and requirements of iron in the human. *J. Amer. med. Ass.*, **162,** 197.

(6) Davidson, S., and Richmond, J. (1958). Cost of oral iron preparations in family and hospital practice. *Lancet*, (*ii*), 570.

(7) Kerr, D. N. S., and Davidson, S. (1958). The prophylaxis of iron-deficiency anæmia in pregnancy. *Lancet*, (*ii*), 483.

(8) Demulder, R. (1958). Iron: metabolism, biochemistry and clinical pathological physiology—a review of recent literature. *Arch. intern. Med.*, **102,** 254.

Chapter 25

VITAMINS A, B, C AND D

MAN cannot synthesise any vitamins in his body unless activation of some steroids in the skin to form vitamin D is considered as synthesis. Lack of a particular vitamin may lead to a specific deficiency syndrome, *e.g.* scurvy (vitamin C) or beri-beri (vitamin B). However, diets may be deficient in several vitamins at the same time so that complex multiple deficiency states occur. In such cases therapy with all the important vitamins is indicated. It has frequently been suggested, but never proved, that subclinical vitamin deficiencies are a cause of much chronic ill-health and liability to infections. This idea has led to enormous consumption of vitamin preparations which probably have no more than placebo value. Fortunately most of the vitamins are comparatively non-toxic, but prolonged administration of vitamins A and D can have serious ill-effects.

Vitamins fall into two groups:—

1. The water-soluble vitamins, the B group and C.
2. The fat-soluble vitamins, A, D, K and E.

VITAMIN A

Deficiency of vitamin A leads to defective vision in dim light and to metaplasia and hyperkeratosis of epithelia throughout the body, which is especially serious on the cornea, leading to xerophthalmia and keratomalacia.

The Functions of Vitamin A. Vitamin A forms part of the light-sensitive protein, rhodopsin, present in the rods of the retina. The part played by vitamin A in the maintenance of epithelia is unknown. Since epithelia damaged by vitamin A deficiency are vulnerable to infection the reputation of vitamin A to be the "anti-infectious" vitamin has some basis of fact, but there is no evidence that vitamin A protects normal people against infection.

Sources of Vitamin A. Carotene is converted into vitamin A in the intestine, hence green vegetables and carrots are satisfactory dietary sources, and so are milk, cheese, butter, eggs and liver. Margarine has vitamin A added to it. Fish-liver oils are recommended for babies on account of their vitamin D content, but they are also very rich sources of vitamin A.

Requirements of Vitamin A are about 3,000 International Units a day for an adult. 5,000 I.U. may be desirable during pregnancy and lactation. A normal Western European diet contains adequate amounts of vitamin A or carotene, but deficiencies are relatively common in Asia. Vitamin A is stored in the liver, which, in normal individuals, contains enough to last for 1 to 2 years.

Indications for Vitamin A therapy are the prevention and cure of the deficiency state. Vitamin A is fat-soluble and, like fats, is poorly absorbed in steatorrhœa and similar conditions. The standardised vitamin A absorption test has been made the basis of a test for steatorrhœa. Once a deficiency has been diagnosed, 50,000 units of vitamin A should be given daily by mouth, and should be continued until the patient recovers. Vitamin A may benefit the hyperkeratosis of psoriasis. Capsules of the pure vitamin and of fish-liver oil are available.

Toxic Effects of Vitamin A occur if very large amounts are taken (in children 75,000 to 500,000 I.U. daily). A diagnostic sign is the presence of painful tender swellings over the bones. Acute toxic symptoms include drowsiness and vomiting; after 24 hours the skin begins to peel. Anorexia, skin lesions and general malaise also occur. Most cases of vitamin A poisoning have been due to mothers administering large amounts of fish-liver oils to their children in the belief that it was good for them. Arctic explorers have been made very ill after eating the livers of arctic carnivores which contain about 20,000 I.U. of vitamin A per gram.

The Vitamin B Complex

The name "Vitamin B" was originally given to a dietary factor which was necessary for the growth of rats. It was soon shown not to be a single compound. A number of widely differing substances are now, for convenience, included in the vitamin B complex:—

Aneurine (B_1), *riboflavine* (B_2), *nicotinamide* and *pyridoxine* (B_6) are discussed here; for *folic acid* and *cyanocobalamin* (B_{12}), see Chapter 24.

Pantothenic acid, *inositol*, *biotin*, and *para-aminobenzoic acid* are not known to be of practical clinical importance as recognisable deficiency states do not occur in man. *Choline* is usually included in the B group of vitamins, although it can be synthesised in the body if sufficient methyl groups are available (*e.g.* from methionine). Choline deficiency in animals leads to accumulation of fat in the liver, and it has been given to patients with Laënnec's hepatic cirrhosis in an attempt to reduce the fatty infiltration. There is little evidence that it does any good.

The B group vitamins are all soluble in water and many of them are concerned in essential oxidation-reduction reactions; yeast and liver are rich sources of most of them and they are synthesised to a variable extent by bacteria normally present in the colon. An abnormal colonic flora (*e.g.* after antimicrobials) may lead to diarrhœa, sore mouth and lesions of the mucous membranes which occasionally respond to administration of the B group vitamins.

Vitamin B deficiencies are common only in places where chronic malnutrition is common, but alcoholics usually, and food faddists sometimes, eat diets deficient in vitamin B. In a number of chronic gastro-intestinal diseases, including steatorrhœa, vitamin intake or absorption may be inadequate. Patients maintained by intravenous feeding for more than 2 days need the B vitamins. There are a large number of proprietary preparations of the B group vitamins as well as those in the B.N.F. which are:—

Vitamin B Compound Tablets:—

aneurine hydrochloride	1 mg.
riboflavine	1 mg.
nicotinamide	15 mg.

Dose: Prophylactic, one or two tablets daily.

Vitamin B Compound Tablets, Strong:—

aneurine hydrochloride	5 mg.
riboflavine	2 mg.
nicotinamide	20 mg.
pyridoxine	2 mg.

Dose: For the treatment of vitamin B deficiency, one or two tablets, thrice daily.

Aneurine (Vitamin B_1, Thiamine)

Gross deficiency of aneurine leads to beri-beri which is characterised by peripheral neuritis, high-output cardiac failure, œdema and, rarely, demyelination of the central nervous system (Wernicke's encephalopathy).

History of Aneurine

Beri-beri is largely a man-made disease: it became common in the East only when steam mills were developed in the mid-19th century and polished rice (*i.e.* rice without its inner husk) replaced brown rice as the staple diet. Beri-beri occurred in up to 40% of Japanese naval ratings, but was almost abolished by the introduction of a more varied diet. In 1909 an experiment was performed on 300 healthy Javanese labourers building a railway in Malaya. They all preferred polished rice, for its superior taste, and ate it even though it was explained that they might get beri-beri. Half of them, chosen at random, were given polished rice, and the remainder brown rice. After 3 months beri-beri began to develop in the group eating polished rice, but not in the other. The groups were switched after 6 months and beri-beri immediately improved when the victims ate the brown rice. Correspondingly, the previously unaffected group began to develop beri-beri now that they were eating polished rice. In all, 20 cases of beri-beri developed on the polished rice diet, as compared with none amongst those eating brown rice. It was soon realised that the anti-beri-beri factor and the "vitamin B" necessary for growth in rats were similar. Aneurine was synthesised in 1936.

Function of Aneurine

Aneurine phosphate is the co-enzyme of carboxylase, and is required for normal carbohydrate metabolism. In its absence the substrates of carboxylase (pyruvic and other α keto-acids) cannot be metabolised, and so they accumulate. Despite detailed knowledge about its function as a co-enzyme, it is still not known how a deficiency of aneurine leads to the characteristic symptoms of beri-beri.

The Pyruvate Metabolism Test for aneurine deficiency is performed by measuring blood pyruvate before and after taking glucose by mouth. An abnormal rise in the blood pyruvate usually indicates aneurine deficiency, but may also occur in heavy-metal poisoning.

Sources and Requirements of Aneurine. Aneurine is very widely distributed in plants and animals. The outer coats of grain kernels are rich in it, but these are removed in the preparation of white flour or polished rice. Requirements of aneurine vary directly with the amount of carbohydrate consumed, but 0·5 mg. aneurine for every 1,000 Calories is about enough.

Indications for Aneurine

Vitamin deficiencies are almost always complex and although beri-beri is primarily due to a deficiency of aneurine, diets chiefly consisting of polished rice are also deficient in riboflavine, nicotinamide, pyridoxine, vitamins A and D, and generally of protein as well. Thus a general improvement in diet is desirable in addition to the specific treatment with aneurine. In Western countries beri-beri is rare and often atypical, it is due either to a bizarre diet or to malabsorption from the gut. Aneurine is destroyed readily in an alkaline medium and hence deficiency is particularly likely to occur in achlorhydric patients. Other causes of aneurine deficiency include chronic diarrhœas occurring in such diseases as ulcerative colitis, steatorrhœa, carcinomatosis, excessive vomiting of pregnancy and other chronic gastro-intestinal diseases. Requirements are increased whenever metabolism is increased, for instance in hyperthyroidism or prolonged fever. Aneurine deficiency should always be considered as a possible cause of obscure peripheral neuritis or high-output cardiac failure. Alcoholic polyneuritis sometimes responds to large doses of vitamin B complex; spirit-drinking alcoholics who take most of their calories in the form of alcohol (which requires aneurine for its metabolism) and do not eat enough aneurine-containing food, may develop beri-beri heart failure.

For severe beri-beri 25 mg. of aneurine hydrochloride should be given daily i.m. or i.v. For prophylaxis, 2 mg. daily by mouth is adequate.

Toxic Effects of Aneurine are very rare, but occasionally a patient becomes sensitised to aneurine preparations.

Riboflavine (Vitamin B_2)

Deficiency of riboflavine leads to angular stomatitis, ulceration of mucous membranes, "magenta" tongue, vascularisation of the cornea and seborrhœic dermatitis, especially of the face. It is very rare in Britain, but occurs in areas where chronic malnutrition is widespread. It usually accompanies other deficiency diseases, such as beri-beri, pellagra, kwashiorkor. Riboflavine deficiency predisposes to snow-blindness.

Riboflavine is an essential component of certain oxidative enzyme systems.

Daily requirement is about 2 mg. If a deficiency of riboflavine is suspected a therapeutic test may be performed; improvement of the lesions within a week of giving riboflavine in the absence of other therapy suggests that the lesions were in fact due to its deficiency.

The usual therapeutic dose is 5 to 10 mg. a day orally, but parenteral preparations are available. Toxic effects do not occur.

Nicotinamide (Nicotinic Acid Amide)

Deficiency of nicotinamide leads to pellagra, which is a generalised disease affecting especially the whole gastro-intestinal tract (diarrhœa, red inflamed tongue, gastritis), the central nervous system (dementia), the skin, especially where it is exposed to light (dermatitis). It occurs in underfed populations, particularly where maize is a staple food.

Nicotinamide is an essential part of co-dehydrogenases I and II, and so it is present in every living cell. Tryptophan, which is present in good quality protein, can be converted into nicotinamide, and consequently will substitute for it in the diet. Maize protein is conspicuously lacking in tryptophan.

Daily requirement is about 20 mg. Pellagra is not usually a pure nicotinamide deficiency, so the other B vitamins and ascorbic acid should be given too. The dose is 250 to 500 mg. orally daily in divided doses. Parenteral preparations are available.

Toxic effects do not occur with nicotinamide. Nicotinic acid, although it is as effective as nicotinamide in the treatment of pellagra, causes peripheral vasodilatation which is accompanied by an unpleasant flushing and itching, and the patient may faint.

Pyridoxine (Vitamin B_6)

Pure pyridoxine deficiency is very rare. It is only likely to occur in infants on peculiar artificial food. Convulsions and anæmia with dermatitis and other symptoms similar to those of pellagra occur. The anæmia, which is hypochromic and microcytic, does not respond to iron; it is due to defective hæmoglobin synthesis. Adults probably require 1 to 2 mg. pyridoxine a day in the diet. The therapeutic dose is up to 100 mg. of the hydrochloride per day orally or by injection. It is advocated in vomiting of pregnancy and in radiation sickness.

ASCORBIC ACID, VITAMIN C

Deficiency of ascorbic acid leads to scurvy, which is characterised by petechial hæmorrhages, hæmatomas, bleeding gums (if teeth are present), anæmia and, in children, cessation of ossification in the growing-ends of bone.

History of Ascorbic Acid

Scurvy had been a scourge for thousands of years. In the Middle Ages it was treated with a great variety of preparations, among them citrus fruit and fresh vegetables. In 1753 Dr. James Lind performed a simple therapeutic trial on twelve sailors with advanced scurvy. They were all on the same basic diet and were living in the same quarters on board ship at sea. He divided them into pairs and dosed each pair differently. The respective daily treatments were:—

1. cyder
2. sulphuric acid
3. vinegar
4. sea-water
5. a concoction of garlic, mustard, balsam and myrrh
6. two oranges and a lemon

The pair receiving the oranges and lemon recovered and were back on duty within a week; of the others, only the pair taking cyder were slightly improved. Lind also recognised the antiscorbutic properties of green vegetables and salads. The efficiency of oranges and lemons in the prevention and cure of scurvy was repeatedly confirmed; but 40 years were to pass before any attention was paid and a regular daily allowance of lemon juice provided in the Navy. Unfortunately lime juice was soon substituted for lemon juice because it could be had cheaply in the West Indian Colonies. Lime juice contains only about a third as much ascorbic acid as lemon juice and failed to prevent scurvy completely. Synthetic ascorbic acid has been available since the 1930's.

The Function of Ascorbic Acid

It is a powerful reducing agent and probably plays a part in intracellular oxidation-reduction systems, but its exact function is unknown. In scurvy there is a general breakdown of collagenous connective tissue, which explains the main symptoms. Ascorbic acid is also needed if conversion of folic acid to its biologically active form, folinic acid, is to be rapid. It is present in high concentration in the adrenals and it may be involved in steroid synthesis. Only man, monkeys and guinea-pigs get scurvy, other animals are able to synthesise ascorbic acid for themselves.

Ascorbic Acid Saturation Tests. If the urine contains more ascorbic acid than 10 mg. per litre in the absence of treatment, then scurvy is not present. Any excess ascorbic acid, once the body is saturated, is excreted in the urine and this is the basis of the saturation test. If a normal person is given 700 mg. of ascorbic acid daily, then the urine will contain more than 350 mg. per day before the end of 3 days. If it does not, scurvy is possible, but not proved.

Sources of Ascorbic Acid

These are mainly fresh fruit and vegetables, although meat and milk contain a little. Ascorbic acid is rapidly oxidised and destroyed by heating in the presence of air, hence deep-fried potatoes contain more ascorbic acid than do boiled. Properly canned fruit and vegetables retain a high proportion of their ascorbic acid. Orange juice is commonly given to babies for its ascorbic acid content, but sometimes they vomit it and either rose-hip syrup or pure ascorbic acid is used instead.

The Requirement of Ascorbic Acid is about 30 mg. daily for an adult. Maintenance of full saturation of the body requires about 100 mg. a day, but there is little evidence that full saturation is necessary. Pregnancy, lactation, active growth or severe disease increase utilisation of the vitamin. Human milk contains 3 to 4 times as much ascorbic acid as cows' milk, in which the amount is also reduced by pasteurisation or other heat treatment. Hence scurvy is not uncommon with prolonged bottle-feeding of babies unless a supplement of ascorbic acid is added. It also occurs among elderly widowers living alone on bread, bacon, cheese, margarine and tea. Old-fashioned diets for patients with peptic ulcer were liable to be deficient in ascorbic acid. Wound healing is delayed in scurvy, hence ascorbic acid supplements may be desirable in wounded patients who are decrepit or who have been eating abnormal diets.

Indications for Ascorbic Acid are:—

The prevention and cure of scurvy.

Methæmoglobinæmia, for its properties as a reducing agent (see below).

To treat florid scurvy 1 G. daily can be given. 100 mg. daily is enough to prevent development of a deficiency. Ascorbic acid is water-soluble and is usually given orally. Parenteral preparations are available.

Toxic Effects do not occur.

Methæmoglobinæmia

Administration of a reducing substance is required to convert the methæmoglobin back to oxyhæmoglobin. In chronic "idiopathic" forms ascorbic acid 100 to 300 mg. orally twice a day may suffice. In acute or severe cases the ascorbic acid may be given i.v., but methylene blue, 1 to 2 mg./Kg., i.v., is more effective. In chronic forms oral administration of methylene blue may be combined with the ascorbic acid if necessary.

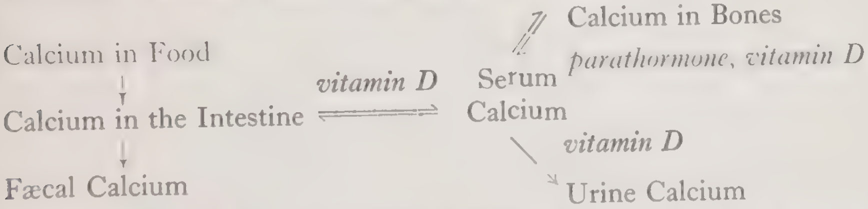
The following substances may cause methæmoglobinæmia: phenacetin, sulphonamides, bismuth subnitrate, nitrites, nitrates (may occur in well water), pamaquine, primaquine, sulfones, acetanilid, phenazone, chlorates, aniline, nitrobenzene.

Sulphæmoglobinæmia cannot be treated by drugs.

VITAMIN D, CALCIUM AND PARATHORMONE

Deficiency of vitamin D leads to rickets in growing children and to osteomalacia in adults.

Calcium. The skeleton contains about 1,200 G. of calcium (all the rest of the body contains only about 12 G.), and provides a reserve which is drawn upon to maintain the serum calcium as near the normal level of 10 mg./100 ml. as possible; about half of this is normally in the ionised form. Calcium is incompletely absorbed from the small intestine, the amount absorbed being dependent on vitamin D. Calcium is lost from the body in the fæces (fæcal calcium is mostly the non-absorbed fraction from the food, but some is excreted into the intestine) and to a small extent in the urine. Calcium metabolism may be represented:—



A daily intake of 1 G. of calcium is normally adequate but this should be doubled in pregnancy and lactation, and during the treatment of rickets and osteomalacia.

Parathyroid Hormone maintains a normal plasma calcium level. It causes calcium release from bones and increases phosphate excretion by the kidney. Impure parathyroid preparations are available and may be useful for the treatment of acute hypocalcæmic tetany in order to avoid repeated injections of calcium gluconate, but tolerance soon occurs. They are in no sense alternatives to the D vitamins which are both more reliable and more effective in chronic hypoparathyroidism. Owing to the slow action of the D vitamins acute hypoparathyroidism is best treated by i.v. injections of calcium (see Tetany, p. 408).

History of Vitamin D

In the early 1920's there were two theories about rickets, the older that lack of sunlight caused the disease, the other that it was due to a dietary deficiency. Both were correct and were reconciled when it was shown that irradiation of food increased its antirachitic activity. The increased sensitivity to rickets of negroes living in temperate climates is at least partly due to their skin pigment preventing the comparatively small amount of sunlight that they receive from activating ergosterol in the skin. There are a large number of chemically related compounds with vitamin D-like activity. Those therapeutically important are :—

$$\left.\begin{array}{l}\text{Calciferol (D2, ergocalciferol)}\\ \text{Activated 7-dehydrocholesterol}\\ \quad\text{(D3, cholecalciferol)}\end{array}\right\}\text{Vitamin D.}$$

Dihydrotachysterol (A.T. 10)

Vitamin D_1 has been shown to be a mixture.

The Functions of Vitamin D

These are complex, the chief being to promote the absorption of calcium from the small intestine, and thus make it available for bone formation; secondary effects are promotion of bone calcification and increase of renal calcium excretion. If there is a deficiency of vitamin D growing osteoid tissue does not become calcified, and rickets results. An adult, who is not growing, needs much less vitamin D than a child, but a chronic deficiency over many years leads to skeletal decalcification, *i.e.* osteomalacia. Women kept indoors on inadequate diets, and who bore many children, used to suffer from osteomalacia (the fœtus and infant being parasitic upon the mother for both vitamin D and calcium). Nowadays, except in poorly fed populations, osteomalacia usually follows metabolic disorders which appear to produce an increased requirement for vitamin D, for instance steatorrhœa, renal failure, and certain inherited diseases.

Sources and Requirements of Vitamin D

Milk, liver and egg-yolk are the best sources, but an ordinary diet may not provide enough vitamin D for a growing child, unless he is exposed to much sunlight. 10 μg. (400 I.U.) per day of vitamin D are normally adequate for children; most baby-foods have enough vitamin D added to them by the manufacturers. Fish-liver oil is a usual source for children, some of whom appear not to dislike it. Premature babies require at least 20 μg. daily as they are particularly liable to rickets. Adults do not normally need more than 2·5 μg. daily, and this is present in a normal diet. Pregnant and lactating women should take about 20 μg. daily.

Indications for Vitamin D

These are the prevention and cure of rickets and osteomalacia. Dihydrotachysterol does not cure rickets in rats, though it does in man; D_2 or D_3 are satisfactory, though they take longer to act. Rarely, when a patient is "resistant" to all the D vitamins, very high doses may be required. A patient may become insensitive to a particular vitamin, say D_2, but remain sensitive to another, D_3. Lupus vulgaris used to be treated with massive doses of vitamin D, which frequently caused toxic effects; chemotherapy with isoniazid gives better results with greater safety (p. 67).

In Steatorrhœa absorption of calcium from the intestine is impaired. This can be remedied by giving large amounts of vitamin D by mouth or parenterally. The simple explanation that vitamin D is fat-soluble and hence not absorbed in steatorrhœa is not tenable, as at least 50% of the fat *is* absorbed and this should carry adequate amounts of vitamin D.

Rickets or Osteomalacia Secondary to Renal Disease is just as obscure as is rickets in steatorrhœa. Supplements of vitamin D improve absorption of calcium from the intestine and allow recalcification of the skeleton.

The dose of vitamin D to cure the metabolic forms of rickets varies according to the cause, an ordinary dose being 1·25 mg. of calciferol (D_2) or D_3 daily, or 1 to 3 mg. of dihydrotachysterol, daily. Parenteral preparations of the D vitamins are available.

Toxic Effects of Vitamin D

These are due mainly to the excessive rise in serum calcium which is provoked. General effects include malaise, drowsiness, nausea, abdominal pain, thirst, constipation and loss of appetite. Other long-term effects include ectopic calcification almost anywhere in the body, renal damage and an increased calcium output in the urine (giving a strongly positive Sulkowitch test); renal calculi may be formed. Patients with sarcoidosis are abnormally sensitive to vitamin D, possibly even to the tiny amount present in a normal diet. Cortisone antagonises vitamin D by an unknown mechanism and has been suggested in the treatment of hypercalcæmic sarcoidosis and of severe hypervitaminosis D.

Tetany

A low serum ionised calcium increases the irritability of the nervous system generally.

Alkalosis (*e.g.* from vomiting in pyloric stenosis) causes tetany partly by lowering the proportion of ionised calcium in the extracellular fluid. The commonest cause of tetany is probably hysterical overbreathing, leading to respiratory alkalosis. Rebreathing from a bag or administration of 10% carbon dioxide in oxygen will help in such a case. Sedation may be necessary to stop the overbreathing. If the tetany follows removal of, or damage to, the parathyroid glands or removal of a parathyroid tumour, repeated i.v. injection of calcium gluconate will be required. The characteristic position, with flexed limbs, may make the usual antecubital site inaccessible, but the veins on the back of the hand are usually practicable. Very severe rickets or osteomalacia may also cause tetany. Calcium gluconate is given slowly i.v. in the acute case, but vitamin D is used for long-term treatment.

Calcium Gluconate is given i.v. as a 10% solution, 10 to 20 ml. being given at the rate of about 2 ml. per minute and repeated as necessary. It must not be given i.m. as it is painful and causes necrosis.

Toxic Effects of Intravenous Calcium may be very dangerous. An early sign is tingling in the mouth and a feeling of warmth spreading over the body. Serious effects are those on the heart, which mimic and synergise with digitalis; fatal cardiac arrest may occur in digitalised animals and it would seem advisable to avoid i.v. calcium in any patient on digitalis. The effect of calcium on the heart is antagonised by potassium and similarly the toxic effects of a high serum potassium in acute renal failure may be to some extent counteracted with calcium.

Calcium Lactate tablets 10 G. daily, can be given if it is desired to supplement the dietary calcium intake.

VITAMIN E (THE TOCOPHEROLS)

Vitamin E is an antisterility vitamin in rats; a corresponding deficiency disease does not occur in man. It has been used with doubtful benefit in a wide variety of conditions.

Guide to Further Reading on the Vitamins

(1) Sebrell, W. H., and Harris, R. S. (1954). The Vitamins. 3 vols. New York: Academic Press.

(2) Bicknell, F., and Prescott, F. (1947). The Vitamins in Medicine. 2nd Ed. London: Heinemann.

Chapter 26

NUCLEOTOXIC DRUGS

The Chemotherapy of Malignant Disease

ALTHOUGH drugs are now the treatment of choice in certain malignant diseases, only temporary remissions and palliation have so far been achieved. However, in the elderly this may last long enough for the patient to live a normal life until he dies of something else.

The term "chemotherapy" of malignant disease has become established, partly because of the parallel* between a neoplastic cell and a bacterium. "In a sense, the cancer cell fulfills Koch's postulates: it can always be demonstrated in the lesion in question; it can be cultivated outside the body, and when reinoculated into an animal it will reproduce the disease. A further similarity is to be found in the manner in which both bacteria and cancer cells develop resistance to chemotherapeutic agents initially able to restrain their growth. The analogy breaks down when pressed too far. . . . Nevertheless, the parallel provides a helpful basis for chemotherapeutic research" (*1*).

The original nucleotoxic drugs were found empirically during research into war gases, but have been improved upon by much systematic synthesis and testing. The partial success achieved has been virtually confined to therapy of malignant diseases of the blood-forming tissues. The drug treatment of hormone dependent neoplasms is discussed in Chapter 21.

Some depression of the normal elements in the bone marrow by nucleotoxic drugs is inevitable and so regular blood examinations to detect over-treatment are desirable whenever these drugs are used.

There are two main groups of nucleotoxic drugs:—

1. **Cytotoxic Drugs**†, which probably act by combining with nucleoproteins. Their effects are very similar to those induced by X-rays. They are useless in acute leukæmias but have a place in the treatment of chronic leukæmia and lymphoma. The group includes:—

   a. Nitrogen mustards: mustine hydrochloride, trimustine, chlorambucil

   b. Ethylenimines: tretamine, thiotepa

   c. Busulphan

   d. Urethane

---

* RHOADS, C. P. (1956). *Med. Clin. N. Amer.*, **40**, 923.

† Also called antimitotic drugs.

2. **Antimetabolites.** The behaviour of a neoplastic cell presumably depends upon abnormal genes; desoxyribosenucleic acid (DNA) is an essential component of chromosomes, and the DNA content and metabolism of neoplastic cells has been shown to be abnormal. Thus the chemotherapeutic approach to malignancy has recently concentrated on substances likely to interfere with DNA metabolism. The group includes:

a. Folic acid antagonists: aminopterin, methotrexate
b. Purine antagonists: mercaptopurine

Cytotoxic Drugs

Nitrogen Mustards

Nitrogen mustards were synthesised as agents for use in chemical warfare. They resemble mustard gas chemically, but with nitrogen in place of sulphur; hence the name. During an extensive investigation of their properties in the Second World War they were shown amongst other things to cause dissolution of lymphatic tissue. This led to their trial in experimental lymphosarcoma in mice, the results of which were sufficiently encouraging for them to be given to patients with malignant lymphomas. Improvement is usually noticeable in a few days.

Mustine Hydrochloride (mechlorethamine) was one of the first nitrogen mustards studied; it is still used. Its main action is to inhibit mitosis, therefore tissues in which cell division is occurring rapidly are most affected, especially lymphoid tissue and the bone marrow. The best results with it have been obtained in patients with generalised Hodgkin's disease, although if the deposits seem well localised X-ray therapy is generally preferred. Both forms of therapy can be used alternately. Mustine hydrochloride is especially effective in abolishing the pyrexia in Hodgkin's disease. It can be tried in cases of chronic leukæmia resistant to less toxic treatment, but it is useless in the acute leukæmias. In mycosis fungoides and in lymphomas which have extensively infiltrated the skin it often relieves pruritus dramatically, with temporary shrinkage of the lesion. It is sometimes tried in bronchial carcinoma; the improvement is usually transient but may justify risking the toxic effects.

When mustine hydrochloride is dissolved in water it is converted into a very reactive form which is also very unstable. It is therefore supplied as a dry powder and only dissolved immediately before it is injected through a fast running i.v. infusion of 0·9% sodium chloride over a period of a few minutes. Ordinary intravenous injection should be avoided because of the risk of leakage outside the vein, which causes a very severe local reaction, and because greater dilution minimises the risk of venous thrombosis. Care is necessary in handling mustine hydrochloride, as painful lesions will result if it gets into the eye or nose. It has occasionally been given directly into the artery supplying a tumour but this is very seldom practicable. It is too irritant to be given orally or i.m. Within a few minutes of i.v. administration all the mustine hydrochloride has reacted with, and become fixed by, the tissues and practically none is excreted. The initial dose is 0·1 mg./Kg. daily for 4 days, but the same total may be given in only one or two portions, which reduces the total duration of the toxic effects but increases their intensity. Some repeat the course at weekly intervals until either the desired response has occurred or there is evidence of severe bone marrow depression. For long-term therapy courses can either be given at regular, say 6-weekly, intervals, or withheld until there is evidence of relapse.

Systemic reactions, particularly centrally-induced nausea and vomiting, are common from 1 to 14 hours after the dose and chlorpromazine may be given prophylactically as an anti-emetic. An alternative is to use heavy sedation with a short-acting barbiturate. A lymphopenia is produced within a few hours and the depression of the bone marrow leads more slowly to granulocytopenia, rarely to agranulocytosis, and sometimes to thrombocytopenia or anæmia, which may last for up to 3 weeks. Significant leukopenia is obviously a relative contra-indication to nitrogen mustard therapy. Menstrual irregularities, particularly temporary amenorrhœa, may result from the effect of the nitrogen mustard on cell division in the ovary and there is reduction of spermatogenesis. Rashes are not uncommon. Doses large enough to be acutely fatal stimulate both the central and autonomic nervous systems.

Trimustine (Trillekamin) closely resembles mustine hydrochloride. It is given in the same way and dose, with the same precautions, and is probably slightly less toxic.

Chlorambucil (Leukeran, C.B. 1348) is a nitrogen mustard with the great advantage that it can be given by mouth. It is probably the oral nucleotoxic drug of choice at present in chronic lymphatic leukæmia and follicular lymphoma. It is less effective than mustine hydrochloride, probably because the gastro-intestinal effects limit the dose. The initial dose of chlorambucil is 0·2 mg. Kg. daily and it may be given in courses of a few weeks' duration, or continued indefinitely in a maintenance dose of up to 0·1 mg. Kg. daily. Nausea, vomiting and diarrhœa are uncommon with these doses. There is usually a progressive slow fall in the blood granulocytes which may continue for 10 days after the drug has been stopped. Twice-weekly blood counts are desirable initially, both to assess the desired effect on the lymphocytes and the unwanted effect on the granulocytes. When the maintenance dose is established, monthly counts are usually sufficient.

Ethylenimines

The ethylenimines resemble chemically the active substances produced when nitrogen mustards dissolve in water. They have similar actions and toxic effects.

Tretamine (triethylene melamine, TEM) has the advantage that it can be given orally, but its effects are delayed and bone marrow depression, particularly of platelet production, is so severe that it is seldom used.

Thiotepa (triethylene thiophosphoramide) closely resembles the nitrogen mustards in its action and uses, although its effect on the blood count is often delayed for 2 to 3 weeks. It seems to be less toxic than mustine hydrochloride for an equivalent therapeutic effect. The dose is 5 to 10 mg. daily, orally or by i.v. or i.m. injection, until either remission occurs or the white cell count begins to fall precipitously.

Busulphan (Myleran)

Busulphan differs from the other cytotoxic drugs in that it affects, for practical purposes, the bone marrow alone. It is particularly useful in chronic myeloid leukæmia, for which it is the drug of choice. The initial dose is 4 to 6 mg. a day, orally, until the granulocyte count falls to 20,000 c.mm. This is followed by a maintenance dose, usually 2 to 4 mg. daily, sufficient to keep the granulocyte count at around 10,000/c.mm. Benefit is not seen for 2 to 3 weeks. Weekly blood counts are desirable at least initially, because marrow aplasia sometimes occurs. Bleeding due to thrombocytopenia is not uncommon. Busulphan can be used in conjunction with X-ray therapy.

Urethane

Urethane inhibits mitosis, but is much less potent than the nitrogen mustards and is virtually obsolete.

Antimetabolites

Antimetabolites are substances which are sufficiently like a normal metabolite to combine with the same enzymes, but sufficiently different to prevent the usual metabolic reaction. The concept derived from studies of the mode of action of sulphonamides. It was noted as a chance observation that a folic acid analogue accelerated leukæmia in a patient and this stimulated a search for folic acid antagonists. The antipurine drugs were found during a search for antagonists of nucleic acid precursors. The leukæmic process eventually becomes resistant to the antimetabolites; cross resistance develops within both the folic acid antagonist and purine antagonist groups, but not between the groups. The antimetabolites are of use only in acute leukæmia and they can be given together with, or following, adrenocortical steroids.

Folic Acid Antagonists

Aminopterin closely resembles folic acid chemically and blocks both its conversion into folinic acid and also the utilisation of folinic acid. It is used sometimes in the treatment of acute leukæmia in children. Aminopterin is not used in adults, who are less tolerant of it than are children. The dose is 0·2 to 2 mg. daily, orally, for 2 or 3 weeks or until remission occurs. Toxic effects are extremely common and include stomatitis, vomiting, diarrhœa and bone marrow depression leading to bleeding or agranulocytosis. Toxic effects can be reversed by giving folic, or better folinic acid (6 mg. daily) but this, of course, also reverses the effect on the leukæmic process.

Methotrexate (amethopterin) is similar but probably has relatively less toxic effect on the gastro-intestinal tract. The oral dose is 2·5 to 5 mg. daily.

Purine Antagonists

Mercaptopurine (6-mercaptopurine, Puri-Nethol) blocks the synthesis of nucleic acid precursors. It often produces temporary remission in the acute leukæmias of both children and adults. The initial oral dose is 3 to 4 mg./Kg. daily until a remission occurs (3 to 4 weeks), followed by the minimum dose which will maintain the remission. This is continued indefinitely for as long as benefit seems to be obtained. Bone marrow depression is common and so blood counts are necessary, weekly at first. Gastro-intestinal upsets are very much less common than with the folic acid antagonists.

Many other antagonists of nucleic acid precursors are being investigated.

Radio-phosphorus (^{32}P, Sodium radiophosphate)

Phosphorus is concentrated in cells which are dividing rapidly, particularly the bone marrow, which receives most of the β irradiation when ^{32}P is given. The effects are similar to those of whole-body irradiation and there seems little to choose between X-ray therapy and ^{32}P in chronic myeloid leukæmia. In polycythæmia vera ^{32}P is now the treatment of choice. The dose is 2 to 5 millecuries and is usually given intravenously for the greater certainty of this route. The maximum effect on the blood count does not occur for 1 to 2 months after the dose. In polycythæmia yearly treatments often give good control. Excessive depression of the bone marrow is the main unwanted effect.

Phenylhydrazine has been used to produce hæmolysis in polycythæmia vera but it is very toxic and is now obsolete.

Choice of Drug Treatment in Malignant Disease of the Blood-Forming Tissues

The general medical care (*e.g.* blood transfusions, antibiotics) is not discussed here. X-ray therapy is the preferred treatment for well-localised deposits and is an alternative to drugs in the chronic leukæmias, but is worse than useless in acute leukæmias. It remains unknown why certain nucleotoxic drugs are more effective than others in particular malignant conditions; the facts have been established by trial and error. Adrenocortical steroids are used for two purposes in leukæmia; first to influence the primary disease process,* this only occurring with the lymphatic forms; and second, to reduce complications, particularly those due to hæmolytic anæmia and thrombocytopenia. The approximate order of choice of drug for the commoner conditions may be summarised:—

Condition	*Status of radiotherapy*	*Drugs in approximate order of choice*
Acute leukæmia	useless	mercaptopurine adrenocortical steroids methotrexate (in children only)
Chronic myeloid leukæmia	often useful (X-rays or ^{32}P)	busulphan
Chronic lymphatic leukæmia	very useful	trimustine mustine hydrochloride adrenocortical steroids chlorambucil thiotepa
Hodgkin's disease	especially useful for localised deposits	trimustine mustine hydrochloride
Multiple myeloma	may help bone pain ^{32}P	

When, as nearly always occurs eventually, the malignant process becomes resistant to one drug it is reasonable to try another. There is nothing to be gained by giving a second nucleotoxic drug coincidentally, but adrenocortical steroid therapy may be combined with a nucleotoxic drug. There is sometimes discussion as to whether acute leukæmia should be treated at all. Burchenal's remarks about acute leukæmia also apply to most of the chronic conditions: "Too often the attitude of the doctor is that there is no cure for the disease, therefore the child or adult should be allowed to die in peace." The answer to that is fourfold: 1 The untreated patient does not usually die in peace but frequently suffers many of the painful complications of the disease. 2. Under therapy many of these children can live happy lives, continuing in school and playing as normal children; 3. During this time the family have time to adjust themselves to the situation; and 4. Most important—if these patients can be kept alive for another year or two, who can say that some investigator somewhere in the world will not come forth with a really effective agent to control the disease?"*

---

* High doses are used, up to 200 mg. prednisone a day.

---

* Burchenal, J. H. (1954). *Bull. N.Y. Acad. Med.*, **30,** 429.

Guide to Further Reading on Nucleotoxic Drugs

(*1*) Scott, R. B. (1958). The chemotherapy of malignant disease. *Brit. med. J.*, (*i*), 1.

(*2*) Robson, J. M., and Keele, C. A. (1956). Nucleotoxic drugs. *In* Recent Advances in Pharmacology. 2nd ed. London: Churchill.

(*3*) Haut, A., *et al.* (1960). The clinical management of leukemia. *Amer. J. Med.*, **28,** 777.

(*4*) Krakoff, I. H. (1960). Mechanism of drug action in leukemia. *Amer. J. Med.*, **28,** 735.

Chapter 27

DRUGS ACTING ON THE SKIN

In this chapter only the general principles of the use of drugs in dermatology can be discussed, but an outline of treatment of the commoner afflictions is also given in a table on pages 425-428.

It is easy to do more harm than good with potent drugs, and this is particularly true in skin diseases, also many skin lesions are in fact caused by systemic or local use of drugs. In patients prone to any allergy it is very easy to provoke further hypersensitivity reactions during treatment.

Local treatment of skin lesions appears to offer a unique opportunity for the trial of different treatments on similar lesions in the same individual at the same time, but substances applied locally are sometimes absorbed and may exert effects on the body as a whole. Another difficulty is that the healing of a lesion at one site, for some unknown reason, often produces improvement in similar lesions elsewhere, and conversely to provoke a flare-up at one site often makes all the other lesions worse as well. Thus the "control" treatment may at first appear to have caused healing or exacerbation that is in fact due to the effects of the more active substance applied to the opposite side. Substances that are well absorbed from intact skin are usually soluble in both water and fats; those completely insoluble in either are not absorbed. Fats and oils enter the skin mainly through the hair follicles and sebaceous glands. From inflamed areas most substances are absorbed to some extent.

The manner in which drugs are applied to the skin is often important and depends upon the nature of the drug and the desired physical effect; for instance this may be to promote cooling, to reduce evaporation or friction, or to give protection. In general, the more acutely inflamed lesions are readily aggravated by drugs and so simple soothing applications should be employed.

Lotions or wet dressings are usually used to cleanse and cool acutely inflamed lesions, especially where there is much exudate. The initial application, and the cooling effect of evaporation of the water, is thought to reduce the inflammatory response by inducing superficial vasoconstriction. Oils are sometimes used to cleanse skins intolerant of soaps. 0·9% sodium chloride solution, Lead Lotion, B.P.C., or Aluminium Acetate Lotion, B.N.F., are also frequently used, but milk is satisfactory in emergencies. Soaks of approximately 0·05% potassium permanganate are very satisfactory if the lesion is on the limbs. Lotions containing more active ingredients (*e.g.* ichthammol, coal tar) are sometimes used on subacute lesions, but occasionally these irritate the skin further. The use of lotions or wet dressings over very large areas can reduce body temperature excessively and may be dangerous in the elderly or the very ill.

Shake Lotions (*e.g.* Calamine Lotion, B.P.) are essentially a convenient way of applying a powder to the skin with the additional cooling effect due to evaporation of the water. They are contra-indicated when there is much exudate, because of crust formation. They sometimes produce excessive drying of the skin but this can be reduced if oils are included, as in Calamine Lotion, Oily, B.P.C.

Creams are emulsions either of oil-in-water (cosmetic vanishing creams) or water-in-oil. A cooling effect (cold creams) is obtained with both groups as the water evaporates. Water-in-oil creams (*e.g.* Oily Cream, B.P., Zinc Cream, B.P.) behave like oils in that they do not mix with serous discharges, but their chief advantage over ointment is that the water content makes them easier to spread, and they give a better cosmetic effect. They are especially useful for protecting the skin, *e.g.* when it is chapped or dried, or on babies' buttocks, and can be used on hairy parts. They can be used as vehicles, particularly for fat soluble substances. A dry skin is short of water, not of oil, but oily substances are used to provide a barrier and so reduce evaporation of water and in turn improve the condition of the skin. Oil-in-water creams do mix with serous discharges and are especially useful as vehicles for water-soluble substances, *e.g.* Buffered Cream, B.N.F.

Powders (*e.g.* Zinc Oxide Compound Dusting-powder, B.P.C.) cool by increasing the effective surface area of the skin and they reduce friction between skin surfaces by their lubricating action. They cause crusting if applied to lesions with much exudate. Water repellant powders such as Zinc Stearate Dusting Power, B.N.F., are used for dusting babies.

Ointments (*e.g.* Simple Ointment, B.P., Zinc Ointment, B.P.) are mixtures of greases and fats virtually free of water. They adhere firmly, giving protection but preventing both evaporation of fluids and heat loss. Thus although they are helpful in chronic conditions to soften crusts and as vehicles, *e.g.* Emulsifying Ointment, B.P., they are not used in acute conditions where free removal of exudate and cooling are needed. They are difficult to remove except with oil or detergents, and are messy and inconvenient, especially on hairy parts.

Barrier Creams of many different kinds have been devised for special purposes in industry in an attempt to reduce occupational dermatitis. They may make cleansing the skin after dirty work easier and more efficient. They are not usually very effective, because it is impossible to maintain the barrier complete. Another disadvantage is that workers may become sensitised to substances in the barrier creams.

Pastes (*e.g.* Zinc Gelatin, B.P. (Unna's paste), Zinc Compound Paste, B.P.) are ointments containing insoluble powders. They are very adhesive and give good protection. Their powder content enables them to absorb a moderate amount of discharge. They are used as vehicles (*e.g.* Coal Tar Paste, B.P.C., which is Zinc Compound Paste with 3·5% coal tar).

Caustics are used to destroy unwanted tissue, including warts and corns. Great care is obviously necessary to avoid ulceration. They include trichloroacetic acid (10 to 20%), silver nitrate sticks, salicylic acid (10 to 50%) and many others. Podophyllin (15%) is used for similar purposes but may act as an antimitotic rather than as a caustic.

Keratolytics are mild caustics and are used for softening and removing the horny layer of the skin. They are all liable to damage normal skin and should therefore be confined to the lesion as far as possible. If used too strong or for too long they may cause ulcers. They are used particularly in the chronic scaling conditions, especially psoriasis. Salicylic acid, about 2%, is probably the first choice as in Salicylic Acid Ointment, B.P. or Zinc Oxide and Salicylic Acid Paste, B.P. (Lassar's paste). Dithranol (0·1 to 1%) has an almost specific effect on psoriasis, leading to replacement of the parakeratosis by normal epithelium. This seems to be associated with the marked erythema dithranol produces rather than with a keratolytic effect. It may cause severe reactions, as may resorcinol (2 to 20%) which in addition can cause myxœdema if absorbed from the skin.

In weaker strengths keratolytics are sometimes effective antipruritics, presumably by a counter-irritant effect.

Tars are mildly antiseptic, antipruritic and are comparatively safe in low concentrations (up to 5%). They both prevent and reverse parakeratosis. There are very many preparations, which usually contain other substances, *e.g.* Ammoniated Mercury and Coal Tar Ointment, B.P.C., Zinc Oxide and Coal Tar Paste, B.P.C. (White's Tar Paste). Ichthammol is a sulphurous tarry distillation product of fossilised fish (obtained in the Austrian Tyrol), it is used as a mild antiseptic, Ichthammol Ointment, B.P. Tars increase the sensitivity of the skin to sunlight.

Cosmetics cannot be discussed here, but a comprehensive documented account is available (*1*).

Insect Repellants. Dimethyl or dibutyl phthalate last for some hours; they act by making the skin unpleasant to the insect rather than by odour, so that all exposed skin should be treated.

Insect Bites and Stings. Pain-producing substances in insect bites and stings include histamine, 5-hydroxytryptamine and various kinins as well as formic acid. These probably also account for much of the local inflammatory reaction; systemic reactions may be due to other potent toxins or to allergic reactions (for treatment, see p. 445). Although bee venom is acid and wasp venom alkaline or neutral, it is doubtful if the traditional use of alkali such as ammonia, bicarbonate, or washing blue on bee stings or vinegar or lemon juice in wasp stings has much more than a cooling and placebo effect. Antihistaminics used locally may relieve the itch, partly by their local analgesic action. Severe septic bites may require systemic antibiotics.

Protective Dressings include Flexible Collodion, B.P., and there are many convenient proprietary preparations. Aluminium Compound Paste, B.P.C., is used to protect the skin around colostomies and fistulæ. Silicone barrier creams are also used for this purpose and in the prevention of bed-sores, where their use may save nursing time without detriment to the patient.[*]

Eye Washes, 0·9% sodium chloride is safe and probably as effective as the traditional boric acid washes. Sodium Bicarbonate Eye Lotion, B.P.C., may be more effective in removing discharges. Many antibiotics, adrenocortical steroids, local anæsthetics and other drugs are available in convenient preparations for use in the eye. These are used according to the general principles discussed elsewhere.

Mouth-washes are mainly useful for their physical effect in cleaning the mouth and for the clean taste that they leave. However, most are also mild antiseptics. They include Compound Glycerin of Thymol, B.P.C., Phenol and Alkali Mouth-wash, B.P.C., and many others. Antibiotic lozenges often do more harm than good (p. 37).

Gargles are also mainly useful for their cleansing and placebo effects *e.g.* Potassium Chlorate and Phenol Gargle, B.P.C.

Ear-drops. Chloramphenicol ear drops (5%) are probably the most effective antimicrobial drops. Boric Acid Ear-drops, B.P.C., are so weak as to have little more than a physical and placebo effect. Spirit Ear-drops, B.P.C., are useful for cleansing and drying, Hydrogen Peroxide Ear-drops, B.P.C., are used to loosen wax. There are many others.

Antiseptic Applications *(4)*[†]

The following list includes only some of the many available preparations:—

Dakin's Solution (Surgical Solution of Chlorinated Soda, B.P.) is effective because of the chlorine it liberates. It is useful for cleaning infected wounds. For cleansing skin round infected areas it should be diluted 1 : 4. Eusol is similar, but evolves less chlorine and is less stable.

Cetrimide Solution, B.N.F., contains 1% cetrimide which has a bactericidal action on a wide range of organisms and is an efficient detergent cleansing agent.

---

[*] BATEMAN, F. J. A. (1956). *Brit. med. J.*, (*i*), 554.

[†] For further information see Drugs of Choice 1960-1961, ed. Modell, W. St. Louis: Mosby.

There is a very wide range of mild antiseptics suitable for use on the skin before injections or surgical operations including Cetrimide Solution, B.N.F., Chloroxylenol Solution, B.P., Iodine Solution, Weak, B.P., and Proflavine Solution, B.N.F. These are conventionally preceded or followed by Surgical Spirit, B.P.C.

Antiseptic Ointments and Creams are sometimes useful in chronic conditions where antibiotic preparations may be contra-indicated. They include Cetrimide Cream, B.N.F., Proflavine Cream, B.P.C., Ammoniated Mercury Ointment, B.P., and Mercuric Nitrate Ointment, Dilute, B.P.

Counter-irritants

Counter-irritants are used to stimulate nerve endings in intact skin for the purpose of relieving pain in viscera or muscle supplied by the same nerve root. All produce inflammation of the skin. They are often effective, though how they act is not known; there is no lack of theories. The psychological effect is certainly important and other possibilities are:

1. That vasodilatation at the site of the pain, produced either reflexly or by antidromic stimulation, may promote relief.

2. That the arrival of numerous pain impulses from the skin may alter the effect of impulses from other parts supplied by the same nerve root.

The best counter-irritants are physical agents, especially heat. Many drugs have, however, been used for this purpose and suitable liniments (*e.g.* Camphor Liniment, B.P.), ointments (*e.g.* Methyl Salicylate Ointment, B.P.C.) and poultices (*e.g.* Kaolin Poultice, B.P.) are included in the B.N.F.

Cantharides plasters are used to produce blisters whose base can be used as test sites for experiments with pain-producing substances, but are obsolete as a counter-irritant. Taken orally cantharides irritates locally, but is absorbed and then excreted in the urine, inflaming the urinary tract, which is the basis of its unjustified reputation as an aphrodisiac. Fatal nephritis has often occurred after attempts to use it in this way.*

Mustard plasters are obsolescent as they can cause blisters and ulcers which are very slow to heal.

Aconite does not inflame the skin but specifically stimulates sensory nerve endings, producing a sensation of warmth or tingling. It is a very powerful poison and there seems little point in using it. Two medical students poisoned themselves when they each took a pinch of aconitine in error for vitamin C whilst "engaged in 'spring-cleaning' a privately owned collection of materia medica."†

---

* Editorial (1954). *Brit. med. J.*, (*ii*), 1405.

† FIDDES, F. S. (1958). *Brit. med. J.* (*ii*), 770.

Anti-pruritics

Impulses responsible for the sensation of itching pass along the same nerve fibres as those of pain, but the sensation experienced differs qualitatively as well as quantitatively from pain. Liberation of histamine in the skin causes itching and may be responsible for the itching of urticarial hypersensitivity reactions. Many drugs, especially the morphine group, are known to be histamine liberators; bile salts also release histamine and this may explain some, but certainly not all, of the itching of obstructive jaundice.

As with pain, the removal of the cause is obviously the best treatment and such causes as parasites, infections, diabetes and reticuloses must be considered, but there remain the majority of patients in whom the cause of the itch either cannot be removed, as in some forms of jaundice, or is not known. Scratching or rubbing seems to give relief by converting the intolerable persistent itch into a more bearable pain, and may even cure the itch at the cost of removing the epidermis. A vicious circle can be set up in which itching provokes scratching and scratching leads to skin lesions which itch, as in neurodermatitis. Covering the lesion or enclosing it in plaster so as to prevent any further scratching or rubbing may break the cycle.

In severe pruritus sedation is sometimes helpful during the day and hypnotics are usually required at night. The sedative antihistaminics are possibly the first choice, then chloral and, if necessary, barbiturates. Androgens (*e.g.* methyl testosterone sublingually, up to 25 mg. daily) may relieve the itching of incurable obstructive jaundice, although how they do so is not known and there is considerable risk of side-effects. Chlorpromazine sometimes helps, probably by altering the patient's attitude to the itching, although it is also a mild antihistaminic. Antihistaminics are frequently used in pruritus, but except in urticarial conditions they probably act by their sedative effect when given systemically and by their local anæsthetic action when applied locally. Any cooling application has some antipruritic effect, but a number of substances, such as phenol (0·2 to 2%), menthol (0·2 to 1%) or camphor (0·2 to 5%), are often added because they have a reputation as specific antipruritics. Crotamiton, as a 10% cream or lotion, is reputed to have a specific but unexplained antipruritic action, although it may exacerbate an already inflamed skin; convenient proprietary preparations (Eurax, Teevex) are available. Local anæsthetic creams and ointments, such as benzocaine, are useful if the pruritus is sufficiently limited, but they are liable to cause hypersensitivity reactions. Local hydrocortisone preparations are probably the most effective antipruritics. Grenz rays are also very effective and may be used together with drugs.

Chemotherapeutic Agents on the Skin

While certain antimicrobials which are too toxic for systemic use can be used on the skin, many of those used systemically (penicillin, sulphonamides, streptomycin) are unsuitable for application to the skin because sensitisation, and eventually hypersensitivity reactions, occur. Furthermore, local application of antimicrobials, such as the tetracyclines, may lead to the production of resistant strains of staphylococci, so that as a matter of policy antibiotics less useful systemically ought first to be employed on the skin.

Antibiotic preparations with a wide spectrum of activity include:—

Neomycin ointment, 0·5%
Chloramphenicol cream, 1%
Bacitracin, usually with neomycin (Neobacrin) or with polymyxin B (Polyfax), especially for pyocyaneus infections
Tyrothrycin (Tyroderm) cream, 0·5%

Chlorhydroxyquinolines (Vioform, Quinolor) as creams and ointments are especially used in chronic staphylococcal infections.

Tetracyclines as creams or ointments (0·5 to 2%) can be very effective but their use should be restricted, see above.

Erythromycin, as for tetracyclines.

Nystatin (Mycostatin) is used against yeasts and fungi as pessaries, suspensions or ointments (100,000 units/G.).

Adrenocortical Steroids on the Skin

Adrenocortical steroids, given systemically or locally, have been tried in almost all skin diseases. They are sometimes remarkably effective, particularly where there is an allergic factor; they may act by reducing the response of the skin to injury. Since the cause of the lesion is seldom affected it is not surprising that relapse often follows when they are discontinued. The difficulties and dangers of systemic adrenocortical steroid therapy are sufficient to restrict such use to serious conditions (such as pemphigus and severe generalised exfoliative dermatitis) not responsive to other forms of therapy. However, although local applications can be absorbed from large areas in amounts sufficient to cause sodium retention, they do not often cause systemic disturbances. Cortisone itself is ineffective locally but hydrocortisone and many of its derivatives are effective. Unfortunately adrenocortical steroids impair the natural defences of the skin to infection and for this reason some would say that they should always be used together with a local antibiotic, *e.g.* 0·5% neomycin. Others say that this is only necessary where the lesion is already, or seems particularly likely to be, infected. Most of the broad-spectrum antibiotics can be effectively combined with the steroid for local use, but it is advisable not to incorporate those that are widely used systemically. There are many convenient proprietary preparations. Hydrocortisone lotions and creams are available as well as ointments, the strength can be varied from 0·5 to 2·5%, but the weaker concentrations are usually adequate. Fludrocortisone acetate is similar to hydrocortisone but is ten times more potent, so it is used in a strength of 0·1%. There is some evidence that acetonide derivatives of these steroids cure some lesions which do not respond to the acetates.

Sun-burn

Sun-burn is produced by ultra-violet light of shorter wave length than that which produces tanning. However, increased pigment in the skin does protect against sun-burn. Ideally, preparations should block only the harmful rays and so allow tanning, but prevent burn. It is doubtful if this can be achieved, but there are many proprietary preparations containing menthyl salicylate, p-aminobenzoic acid or quinine, which probably act by screening out a proportion or all the ultra-violet rays. Simple creams are often enough to limit sun-burn to a simple erythema. Treatment of mild sun-burn is usually with a lotion such as Calamine Lotion, Oily, B.P., and in severe cases hydrocortisone lotion or cream are very effective. People intolerant of sunlight are often benefitted by chloroquine (300 to 600 mg. of base, daily) but how it works is not known.

Sex Hormones and the Skin

Androgens stimulate the surface epithelium and the sebaceous glands. Thus they tend to produce hyperkeratosis, seborrhœa and acne. Œstrogens have the opposite effect, dandruff ceases to form, comedones shrink and the growth of coarse hair ceases. These effects only occur at doses which have all the other typical effects and so the use of œstrogens for acne in men is seldom justified. Œstrogen-containing creams are advertised as cosmetics to enable women to look younger than they really are, by preventing and removing facial wrinkles. In women before the menopause there is no evidence that œstrogen-containing creams have a greater effect on the skin than the vehicle alone, unless sufficient is absorbed for systemic effects to occur. Post-menopausal atrophic changes do sometimes seem to be improved by their local use, but seldom to the extent claimed by the manufacturers.

SUMMARY OF THE TREATMENT OF SOME COMMON SKIN CONDITIONS

The table on the next four pages is not intended to give the complete treatment of even the commoner skin conditions but merely to indicate a reasonable approach.

Secondary infections of ordinarily uninfected lesions may require local or general antimicrobials in addition. Analgesics and sedatives may be needed in all the painful or uncomfortable conditions.

One or two applications a day are all that is usually necessary unless common sense dictates otherwise.

X-ray therapy is helpful in many chronic skin conditions, but special experience is required and so it is not included in the table.

Guide to Further Reading on Drugs Used on the Skin

(*1*) Harry, R. G. (1955). The principles and practice of modern cosmetics. Modern Cosmeticology, Vol. 1, 4th ed. London: Hill.

(*2*) Year Book of Dermatology and Syphilology. Chicago: The Year Book Publishers, annually.

(*3*) Wilson, H. T. H., and Edwards, J. H. (1958). A comparison of glycyrrhetinic acid and hydrocortisone ointment. *Brit. J. Dermatol.*, **70,** 452.

(*4*) Lowbury, E. J. L., and Lilly, H. A. (1960). Disinfection of the hands of surgeons and nurses. *Brit. med. J.*, (*i*), 1445, and Editorial, 1489.

(5) Bettley, F. R (1960). Some effects of soap on the skin. *Brit. med J.*, (*i*), 1675.

Condition	*Treatment*	*Remarks*
Boils and Carbuncles (staphylococcal)	Pus evacuated surgically. Dakin's solution or 1% cetrimide for cleansing. Magnesium Sulphate Paste, B.P.C., is a strongly hypertonic dressing to loosen slough. 1% crystal violet paint may help prevent spread to surrounding skin.	Local antimicrobials relatively ineffective. Systemic penicillin may be needed in severe cases and may abort an early lesion. Erythromycin best kept in reserve. Fomentations are liable to spread the infection.
Impetigo and Sycosis Barbæ (mainly staphylococcal)	Antimicrobial ointments (*e.g.* neomycin, chloramphenicol, chlortetracycline) 2 to 3 times a day. Chlorhydroxyquinolines (*e.g.* Vioform) especially useful in chronic cases.	Astringent and antiseptic, lotions obsolete except in resistant cases. Systemic antimicrobials may be needed. Pediculosis may be precipitating factor. For a general account of staphylococcal infection see p. 54.
Erysipelas (streptococcal)	Systemic penicillin.	
Marginal Blepharitis (various organisms)	Ointment containing hydrocortisone and an antibiotic.	
Ringworm, Tinea (various fungi)	Acute lesions need lotions and soaks. Chronic lesions on dry skin: Benzoic Acid Compound Ointment, B.P.C. (Whitfield's ointment), Zinc Undecenoate Ointment, B.P. Sub-acute lesions need only half strengths of these ointments. In flexures (*e.g.* tinea cruris) Magenta Paint, B.P.C. (Castellani's paint) is more satisfactory. Very resistant lesions may respond to 1% dithranol ointment. Fungicidal powders, *e.g.* undecenoate, are helpful together with ointments and foot hygiene in tinea pedis. Griseofulvin is the first fungicide which can be given systemically (p. 51).	Most preparations are both fungicidal and keratolytic, so the cells containing the fungus are removed. In tinea capitis epilation has been replaced by griseofulvin. Clipping the hair short and thorough local treatment of the whole scalp prevent self reinfection. Ringworm of nails is very resistant to everything except griseofulvin.

Condition	*Treatment*	*Remarks*
Monilia	Nystatin ointments or pessaries. Gentian violet paint in the mouth.	
Paronychia (monilial and bacterial)	Nystatin ointment under the nail fold, domiphen bromide, magenta paint or chlorhydroxyquinolines sometimes effective.	Essential to keep fingers dry.
Scabies	Benzyl Benzoate Application, B.P., to whole body below the neck after a bath on two successive days.	
Pediculosis	Dicophane Application, B.P.C., contains 2% dicophane (DDT) and is used for the head. Dicophane Dusting-powder, B.N.F., contains 10% DDT and is used in other areas. In epidemics it can be blown into clothing without undressing the patient.	Dicophane is only toxic if a concentrated oily solution is ingested; tiredness, irritability, muscular fatigue and eventually respiratory paralysis may result.
Drug Eruptions	Cooling applications and antipruritics.	Adrenocortical steroids may be needed. Antihistaminics may be tried systemically.
Eczema and Sensitivity Dermatitis Acute:	Lotions, wet dressings or soaks.	Remove the cause where possible.
Subacute:	Zinc oxide creams or pastes sometimes with mild keratolytics added, *e.g.* Zinc Oxide and Salicylic Acid Paste, B.P. (Lassar's Paste).	Often exacerbated by soap and water. Antihistaminics systemically often tried. Antipruritics (p. 421) may be added to lotions, creams or pastes. Hydrocortisone locally may have dramatic effect temporarily. Stronger keratolytics may be needed.
Chronic:	Zinc Oxide and Coal Tar Paste, B.P.C. (White's tar paste).	
Psoriasis Acute:	Lotions, wet dressings.	All keratolytics may be tried. When they have removed the scales and produced an inflammatory response soothing applications may be needed. Dithranol usually worsens acute progressive cases.
Chronic:	Dry areas: dithranol, strength gradually increased from 0·1 to 1%, Ammoniated Mercury and Coal Tar Ointment, B.P.C. Wet areas: weaker keratolytics. Vitamin A is being tried.	

Condition	*Treatment*	*Remarks*
Herpes Simplex	Mild antiseptics for cleansing. Powder for cover.	Symptomatic treatment and prevention of secondary infection.
Herpes Zoster	Analgesics. Local antibiotics if the vesicles are large or ruptured.	Prevention of secondary infection reduces scarring.
Seborrheic Dermatitis, Dandruff Acute:	Lotions, wet dressings.	Antimicrobials if badly infected. Sulphur in various forms helps the seborrheic state but the reason is not known. Selsun irritates the eyes and is poisonous if swallowed. Local hydrocortisone often helps seborrhea.
Chronic:	Daily use of soapless shampoos, *e.g.* cetrimide 1%. Selsun shampoo contains selenium sulphide. Mild cases need only daily applications of Lotion of Salicylic Acid and Mercuric Chloride, B.P.C. If more severe, 3% sulphur in emulsifying ointment. Very resistant lesions may need keratolytics, *e.g.* Salicylic Acid and Sulphur Ointment, B.P.C.	
Exfoliative Dermatitis	Dimercaprol, if due to a heavy metal. Cooling creams and powders locally. Adrenocortical steroids systemically in severe cases.	
Pemphigus	Adrenocortical steroids systemically.	Oral hygiene very important.
Lupus Erythematosus (*a*) Discoid	Chloroquine sulphate or hydroxychloroquine sulphate (400 to 800 mg. daily in divided dose after meals). Cooling lotions and creams.	Mepacrine is an alternative.
(*b*) Systemic	Adrenocortical steroids.	Some give chloroquine as well.
Scleroderma	Adrenocortical steroids often tried.	Response usually very disappointing.
Rosacea	1 to 2% sulphur in emulsion base.	Flushing makes it worse. Œstrogens for menopausal flushing.
Vitiligo	No safe and reliable treatment.	Ammoidin is toxic and often fails.

Condition	*Treatment*	*Remarks*
Acne Vulgaris	Soap and water. Ointments containing sulphur and mild keratolytics in resistant cases. Systemic antimicrobials if infected. Detergents worth trying.	Bromide and iodide exacerbate acne. Local treatment is to remove the hyperkeratoses which block the sebaceous glands, and generally to reduce the greasiness of the skin.
Dermatitis Herpetiformis	Dapsone 25 to 250 mg. daily. Sulphapyridine 0·25 to 1·5 G. daily. Adrenocortical steroids systemically in resistant cases.	Antipruritics locally as required. Not other sulphonamides; beneficial effect is *not* due to antimicrobial action. Methæmoglobinæmia may complicate dapsone therapy.
Hyperhidrosis	Atropine or propantheline. 5% sodium hexameta phosphate either as a solution or in talc.	Better in theory than practice. The characteristic smell is produced by bacterial action so cosmetic deodorants contain antibacterials rather than substances which reduce sweat production.
Intertrigo	Cleansing lotions. Powders and pastes.	To cleanse, lubricate and reduce friction.
Urticaria, Angioneurotic Œdema	As for hypersensitivity reactions (p. 445).	
X-ray Dermatitis	Hydrocortisone preparations locally.	
Pityriasis Rosea	Antipruritics.	Ultra-violet light of value.
Lichen planus	Antipruritics. Horny thickenings reduced with keratolytics.	Often very resistant to treatment. Hydrocortisone locally gives only temporary relief. Systemic adrenocortical steroids in severe cases.
Lichen Simplex (neurodermatitis)	Antipruritics. Sedatives.	Covering the lesion so as to prevent scratching sometimes breaks the vicious cycle. Grenz rays and hydrocortisone locally of great value.
Alopecia, Baldness	None	No convincing evidence exists that any treatment increases hair growth on the head.

Chapter 28

POISONING AND CHELATING AGENTS

POISONING

THE specific treatment of poisoning due to therapeutic agents is mainly dealt with under the drug concerned. In this chapter the general principles of treatment and miscellaneous specific antidotes are described.

Principles of Treatment of Acute Poisoning

Most emergency treatment of acute poisoning is symptomatic, success depending on a combination of speed and common sense as well as on the poison, the amount taken and the time which has elapsed. Where there is a specific antidote, however, its use is vital, *e.g.* nalorphine against morphine-like drugs, atropine against choline drugs. Stomach washout is usually indicated in all cases where the poison has been swallowed, unless it is a corrosive substance; but common sense dictates that in a patient with strychnine convulsions an anticonvulsant must be given before passing the gastric tube, which might otherwise provoke a fatal convulsion. If respiration is failing, identification of the drug and stomach washout, however desirable, may have to wait until a respiratory stimulant has been administered or artificial respiration commenced. It is worth washing out the stomach even some hours after swallowing a solid drug, for gastric emptying time is unpredictable.

It is essential that the immediate aim be clear for, without this, treatment will not combine maximum efficacy with minimum risk, *e.g.* in narcotic poisoning the aim is to keep the patient oxygenated, to sustain his circulation and electrolyte balance until the poison has been disposed of by the body, and to prevent the development of pneumonia. It is *not* to wake the patient up at once, for this, though satisfying to the physician, may be impossible to achieve without poisoning the patient with convulsant drugs.

The principles of treatment may be stated thus:—

1. Removal of the Poison

a. **External:** wash with water, sodium bicarbonate, vinegar, alcohol, as appropriate.

b. **Internal:** (i) by emesis, in conscious patients only, especially if solids (*e.g.* berries) which might block a tube have been eaten; (ii) stomach washout; (iii) hæmodialysis.

2. Prevention of Further Absorption of the Poison

a. **From an Injection Site:** tourniquet;

b. **From the Alimentary Tract:—**

(i) Specific antidotes which combine chemically with the poison. This is important in the case of acids and alkalies but is probably ineffective in the case of most other substances. Generation of gas in the alimentary tract is undesirable and can be dangerous*; a knowledge of elementary chemistry should suffice to avoid this. Saline purgatives may be useful.

(ii) Non-specific antidotes, mostly demulcents, *e.g.* raw eggs, milk, kaolin, flour and water, activated charcoal.

3. Specific Pharmacological Antidotes

Nalorphine, atropine, antihistaminics or chelating agents, as indicated.

4. Non-specific Pharmacological Antidotes

Anticonvulsants in convulsant, and analeptics in narcotic, poisoning.

5. Alteration of Excretion or Metabolism of the Poison

For example, sulphonamides (high fluid intake and urine made alkaline), bromides (chlorides), methanol (ethanol).

6. "General Supportive Treatment"

This is usually taken to mean measures directed towards maintaining circulation, respiration and electrolyte balance, and to preventing pneumonia in unconscious patients.

The Care of the Unconscious Patient may be summarized:—

a. Specific treatment of the cause of unconsciousness, if possible.

b. Preservation of respiration and oxygenation, by drugs or artificial respiration if necessary.

c. Prevention of hypostatic pneumonia by altering posture of the patient about every three hours and prevention of inhalation of foreign material by posture (head lower than chest) and suction of passages as needed. Chemoprophylaxis of pneumonia by, say, penicillin, is ordinarily employed if the patient has been unconscious more than 12 hours, although the merits of this are dubious (p. 28). It may be better to wait for an infection and treat it than to use antimicrobials and increase the risk of a drug resistant pneumonia.

d. Prevention of starvation, dehydration and electrolyte abnormalities.

e. Prevention of bladder distension.

f. Prevention of bed sores.

---

* Tanner, N. C. (1959). *Proc. roy. Soc. Med.*, **52**, 379.

MISCELLANEOUS ANTIDOTES

Chelating Agents

A chelating agent is any compound which will inactivate a metallic ion by incorporating it into an inner ring structure in the molecule. Chelating agents such as dimercaprol and chelates such as sodium calciumedetate are used clinically in the treatment of poisoning with heavy metals.

Dimercaprol (B.A.L., British Anti-Lewisite) was synthesised during a systematic study of possible antagonists to arsenical vesicant war gases such as Lewisite. Arsenic and other heavy-metal ions are toxic in relatively low concentration, probably because they combine to form a ring structure with two of the —SH groups of essential enzymes. Dimercaprol protects by combining its —SH groups with the heavy metal ions to form relatively harmless ring compounds which are excreted, mainly in the urine. Dimercaprol is therapeutically effective because the ring compound formed with many heavy-metal ions is more stable than is the ring structure that the ions form with enzymes. It is obviously desirable that there should be an excess of dimercaprol available until all the metal has been excreted and, as it is both oxidised in the body and excreted in the urine, repeated administration is necessary.

Dimercaprol is useful and may be life-saving in poisoning with arsenic, mercury, gold or antimony. It is useless in lead poisoning because it does not combine with the metal sufficiently firmly, and in iron poisoning the complex dimercaprol forms is even more toxic than the unchelated ion. Its utility in other even rarer forms of heavy-metal poisoning remains undecided.

Dimercaprol, as 5% solution, is given by deep and painful intramuscular injection. The dose in chronic poisoning is 3 mg./Kg. given 4-hourly for 2 days, 6-hourly on the third day and then 12-hourly for 7 days. In severe acute poisoning the course can be started with 5 mg./Kg. 4-hourly during the first 24 hours.

Toxic effects are extremely common during dimercaprol therapy, particularly with the larger doses. They include nausea and vomiting, lachrymation and salivation, paresthesiæ, muscular aches and pains, urticarial rashes, tachycardia and a raised blood pressure. Gross overdosage may cause overbreathing, muscular tremors, convulsions and coma. The mechanism of the toxic effects is not known, but it has been suggested that the removal of metallic groups from essential enzymes may be responsible. There is an impression from a few cases that toxic effects may be reduced by giving 25 to 50 mg. ephedrine half an hour before the injection of dimercaprol but it is not clear why ephedrine should help, if it does.

In Hepato-lenticular Degeneration (Wilson's Disease) the abnormal accumulation of copper characteristic of the disease can be checked and even reversed by giving repeated courses of dimercaprol i.m., which increases the excretion of copper in the urine. Potassium sulphide, 20 mg. orally, after meals, is often given as well, to reduce absorption of copper from the intestine by forming insoluble copper sulphide. Another chelating agent, penicillamine (dimethyl cysteine) given orally in doses of 0·5 to 1·5 G. daily is said to be more effective in increasing the urinary excretion of copper and is less toxic than is dimercaprol. Copper depletion may halt the progression of the disease but symptomatic improvement is limited by irreversible damage to the central nervous system.

Sodium Calciumedetate (Calcium Disodium Versenate) is a calcium chelate which has revolutionised the treatment of lead poisoning. The chelating agent combines more avidly with lead than with calcium and so the lead chelate is formed in the body and excreted in the urine, leaving behind the relatively harmless calcium. Sodium calciumedetate is given by i.v. infusion, 1 to 2 G. in 1 hour twice a day, usually in 5-day courses, repeated as necessary after a 7-day interval. A second course should be given if urinary coproporphyrin excretion exceeds 250 mcg./24 hours, or if severe signs persist. The symptoms and signs of lead poisoning respond dramatically to this treatment and symptomatic treatment (*e.g.* of lead colic with injections of calcium or with anticholine drugs) is now seldom necessary. Toxic effects are very uncommon but reversible renal damage has been reported. Penicillamine also has been successfully used in lead poisoning.

Cyanide Poisoning

The effects of cyanide poisoning appear so rapidly that in most cases the patient is either dead before treatment can be started or else has taken so little that recovery is inevitable if he is left alone. However, speedy treatment may save an occasional life. Cyanide kills by producing cellular anoxia through respiratory enzyme inhibition. This inhibition is reversible and the cyanide can be removed from the enzyme by combination with methæmoglobin to form harmless cyanmethæmoglobin. Thus treatment requires the production of methæmoglobin. This can be achieved by repeated amyl nitrite inhalations followed as soon as possible by sodium nitrite (0·5 G. in 15 ml., i.v.). This is followed by sodium thiosulphate (12·5 G. in 50 ml., i.v., over 10 minutes) to take up cyanide as thiocyanate. Similarly stomach washouts are best performed with oxidising solutions to convert cyanide to harmless cyanate (*e.g.* 5% sodium thiosulphate, 0·2% potassium permanganate or 3% hydrogen peroxide). Special solutions containing iron have been devised for oral use to reduce the absorption of cyanide when stomach washout is not immediately practicable, but they do not keep and are seldom available except where cyanide is a recognised industrial hazard.

Poisoning with Dinitro-compounds

Dinitrophenol was used for a while in the treatment of obesity because it increases cellular respiration by uncoupling oxidative phosphorylation. Hence the basal metabolic rate is increased and the surplus fat used up. However it was soon abandoned because of serious toxic effects. Other dinitro-compounds with similar metabolic effects are now widely used as pesticides in farms and greenhouses, and occasional cases of poisoning occur when the recommended safety precautions are ignored. The hands, face or hair are usually stained yellow by the poison. Symptoms and signs are mainly those associated with a very high basal metabolic rate. Copious sweating and thirst are early warning signs and may proceed to dehydration with vomiting, weakness, restlessness, tachycardia and deep rapid breathing. Eventually convulsions and coma may occur. Treatment is urgent and consists of cooling the patient and attention to fluid and electrolyte balance. It is essential to differentiate this type of poisoning from that due to cholinesterase inhibitors (pp. 234–235) because if atropine is given to a patient poisoned with a dinitro-compound he may stop sweating and die of hyperpyrexia.

GUIDE TO FURTHER READING ON POISONING

(*1*) JACOBZINER, H. (1959). Causation, prevention, and control of accidental poisoning. *J. Amer. med. Ass.*, **171**, 1769.

(*2*) POLSON, C. J., and TATTERSALL, R. N. (1959). Clinical Toxicology. English Universities Press : London.

Chapter 29

GENERAL PHARMACOLOGY, UNWANTED EFFECTS OF DRUGS

Dosage

The clinician, unlike the pharmacologist, is usually concerned with the individual, and not with groups. He is therefore rather less concerned than is the latter with the shapes of the classical dose-response curves, since for him individual variation is often all important.

Sometimes in therapeutics graded responses are required; for instance, it may be desired to reduce, but not to abolish, intestinal motility or consciousness, and the dose of a drug may have to be adjusted with great care. In other instances a total response is required, for instance in chemotherapy, in which dosage is less individual, for the intention is that it should be "supramaximal" and exceed the effective dose for all the parasites. In chemoprophylaxis, group considerations are paramount and individual variation is not considered when choosing dosage.

In animal work it is usual to calculate dose according to weight, although there is evidence that surface area may be more appropriate. In clinical practice the dose of most drugs is chosen in the light of experience, with little regard to variations in the size of patients, *e.g.* digitalis, diuretics, analgesics, although administration by weight is occasionally used. Children from 1 to 10 years are given, of course, smaller doses than adults, and as a rough guide, Young's formula, dose $= \frac{\text{age of child}}{\text{age of child} + 12} \times$ adult dose will serve. For infants there is no reliable formula and if the proper dose of a drug is not known it must be ascertained, because the risk of intolerance is substantial. This is largely because the mechanisms of metabolism and excretion of drugs are not fully developed in infants (p. 440).

Routes of Administration

The common routes of administration will be familiar to the reader. Routes of choice for each drug for different occasions are referred to throughout the book.

In general, drugs are given orally unless there is a good reason to use another route and they are usually absorbed from the small intestine. Parenteral administration is generally chosen when speed or reliability are especially desired, but there are exceptions, for aminophylline is often given parenterally because full doses are so irritant to the stomach. Some drugs are not absorbed from, or are destroyed in, the alimentary tract (streptomycin, adrenaline, insulin) and such facts determine their route of administration. When drugs are applied topically it is well to remember that enough may sometimes be absorbed to cause systemic effects, as for instance atropine poisoning from eye drops, goitre from resorcinol ointment or systemic effects from hormone creams.

Distribution of Drugs in the Body

Most drugs are distributed throughout the body, but there are exceptions, some of which have clinical importance and these are referred to where relevant: for instance penicillin and streptomycin do not reliably penetrate into the cerebrospinal fluid, but isoniazid and chloramphenicol do; iodide is concentrated in the thyroid gland, lead in bone and chloroquine in the liver. A great many drugs do not penetrate into the brain.

Fate of Drugs in the Body

In general drugs are either oxidised, reduced, conjugated or excreted unchanged. More than one pathway of disposal is common. Sometimes it is the metabolic product of a drug that is active rather than the parent substance (phenacetin, hexamine and to some extent chloral). The rate at which drugs are disposed of by the body is important for it controls the frequency of administration if a steady effect is to be maintained. Generally the time a drug persists in the body in clinically active amounts is indicated in this book by the recommended frequency of administration, but this is not invariable, for some drugs are traditionally given, say, three times a day, when once would be quite adequate, *e.g.* thyroxine, bromide, digitalis. Some detail of the fate of drugs in the body is given in this book where it has clinical relevance. It is important to bear in mind that the effects of a drug may be more intense than expected and persist longer if the organ responsible for metabolism or excretion is damaged. There are countless examples of this in clinical practice and they are most common in patients with hepatic or renal disease, for these are the principal organs of drug metabolism and excretion.

Many drugs are excreted in small amounts in milk but it is rare for this to have significant effect on the breast-fed baby. However, it has been claimed that the following drugs have thus adversely affected the baby: iodide and bromide, alcohol, anthracene purgatives and antihistaminics.

Prolongation of Drug Effect

The most obvious way to prolong a drug effect is to give a larger dose, but an even, as well as a prolonged, effect is usually needed and this is more easily obtained by small frequent doses. Prolongation can also be achieved by delaying absorption (and giving larger doses), or by delaying excretion, examples of which are described below. To prolong drug action by delaying metabolism involves altering the chemical formula of the drug, an example of which is the barbiturate series, or interfering with the metabolic path as by blocking the enzyme responsible for its destruction (anticholinesterases). Delaying excretion is seldom attempted, the only important example being the use of probenecid to block renal tubular excretion of penicillin.

Oral preparations designed to give slow continuous release of drugs in the intestine are becoming popular. The possible advantages are obvious; frequency of medication is reduced, which is convenient for the patient, and a single morning dose is less likely to be forgotten than are 3 or 4 daily doses. Fluctuation in blood-level might be reduced, and nocturnal activity of short-acting drugs might be more easily obtained (*e.g.* anticholine drugs, chemotherapeutic agents). In practice, however, these preparations are unreliable and although dosage may often be imprecise without harm it is vital with drugs such as glyceryl trinitrate that it should be very accurate. If the amount in the long-acting preparation exceeds three times the normal single dose, then that preparation should be viewed with suspicion as liable to give erratic results which could be dangerous (7). The great variability of the functions of the stomach and intestine show why this must be so and why demonstration of even release in *in vitro* tests is irrelevant. One drug manufacturer is said to have "taunted his competitors by preparing a long-acting placebo" (7). Techniques for prolonging action include various pill coatings which may dissolve slowly and only in alkaline media, and so in the intestine rather than in the stomach, or which may dissolve after a certain time in contact with water or only on contact with intestinal enzymes. Chelates, resins and the use of multiple "microspheres" with coatings of differing thicknesses have all been used. Before using one of these preparations it is as well to consider whether it is really required and what may be the consequences of failure to provide evenly sustained action. In epilepsy, for example, they could be serious. The risks are not only of failure of the preparation to give up its drug, but also failure to refrain from giving it up all at once.

It may be mentioned here that drugs that irritate the stomach are sometimes given special "enteric" coatings (varnish, hardened gelatin) to delay disintegration of the tablet until it has reached the small intestine. Many of these "enteric"-coated tablets in fact pass undamaged through the whole intestine. Long-acting, or depôt, injectable preparations are more reliable because the environment in which they are deposited is more constant than can ever be the case in the alimentary tract. The aim with these preparations is to render the drug relatively insoluble and so only slowly dissolved at the site of injection. In general such preparations are chemical variants, or the original drug in oil, wax, gelatin or synthetic media. They include the various insulins and penicillins and oily preparations of adrenaline and vasopressin, also solid tablets of hormones are sometimes implanted s.c. Perhaps the best-known example of prolongation of action by delaying absorption is that of the combination of adrenaline with local anæsthetics.

Reduction of Absorption Time of a drug can be achieved by making a soluble salt, *e.g.* barbiturates, or in the case of s.c. injections, by using hyaluronidase. Hyaluronidase is an enzyme which depolymerises hyaluronic acid, which forms a background substance in normal connective tissue and prevents the spread of foreign substances, *e.g.* bacteria, drugs. By combining an injection with hyaluronidase a drug is enabled to spread rapidly over a wide area and so to be absorbed more quickly.

Cumulation

If a drug has a duration of action of, say, 5 or 6 days (*e.g.* digoxin) and is administered in substantial amount 3 times a day, it is clear that the amount in the body will increase as the days pass, for the intake will exceed the removal of the drug, *i.e.* there is cumulation. Although eventually a plateau will be reached where there is a balance between the amount of drug taken in and the amount of drug disposed of by metabolism or excretion, this may be well above the toxic level. With such long-acting drugs it is sometimes permissible to give heavy doses to begin with rather than to build up the concentration slowly, and this is often done with digoxin. Other drugs so long-acting that cumulation must always be borne in mind are thyroxine and bromide.

Since the occurrence of cumulation is simply a matter of an imbalance between intake and output it is not confined to the very long-acting drugs mentioned above. It will occur with any drug if the administration is large enough and frequent enough. Phenobarbitone and sulphonamides if given every 2 hours could show the same effect over a short period, but as no one wants to give these drugs 2-hourly it is seldom seen; it is the habit of prescribing very long-acting drugs 2 or 3 times a day which makes cumulation relatively common in their case. Any drug will cumulate if its metabolism or excretion are blocked and it is given at the usual intervals, *e.g.* penicillin in the presence of probenecid.

Tolerance

Tolerance is said to have developed when it becomes necessary to increase the dose of a drug to obtain an effect previously obtained with a smaller dose. Acquired tolerance is familiar, especially with the opium group of drugs. There is commonly cross-tolerance between drugs of similar chemical constitution and sometimes between dissimilar substances (alcohol and barbiturates). Acquired bacterial resistance is a form of tolerance of great practical importance.

Synergism and Potentiation

Synergism is said to occur when the similar effects of two drugs simply add up, but it is called potentiation when the effects are greater than would be expected by simple addition. Examples of potentiation are the effect of an anticholinesterase on a choline drug response and chlorpromazine on barbiturates. Alcohol synergises with, but morphine potentiates, ether.

Antagonism

Antagonism occurs when drugs with opposing actions are administered simultaneously. It may be that two drugs simply have opposite pharmacological effects (histamine and adrenaline on the bronchi), or it may be that they compete for the same site of action (morphine and nalorphine).

Tachyphylaxis

Tachyphylaxis is said to occur when there is diminishing response to frequently repeated doses of a drug. It occurs with sympathomimetic amines if the doses are very closely spaced and this can have clinical importance. There is no sharp division between tachyphylaxis and tolerance except that tolerance takes days or weeks to develop and tachyphylaxis minutes or hours.

Mode of Action of Drugs

Little can profitably be said here, for though much is known of drug effects, there is far more that is obscure. The importance of the study of mechanisms of action is that better understanding leads to more intelligent use of drugs as well as to development of better drugs. One important type of action is that called "substrate competition" or "competitive inhibition" and which is exemplified by curare, by nalorphine, and by the antihistaminics. These drugs are relatively inactive themselves when they occupy cell receptors, but they exclude more active substances (acetylcholine in the case of curare and morphine in that of nalorphine) and so antagonise their action. Little is known about these receptors or about how drugs attach themselves to them. Drugs acting by competition usually, but not always, have a chemical resemblance to the drug with which they compete. Some drugs act by interfering with enzyme activity (anticholinesterases, acetazolamide); some act on cell membranes, altering permeability to ions, whilst others act inside the cells themselves.

Specificity of Drug Action

The more specific drugs are, the better, because unspecific drugs are liable to have too numerous actions for convenience. Chlorpromazine is an example of an unspecific drug interfering with numerous enzyme processes. On the other hand some anticholinesterases are highly specific for the enzyme cholinesterase, but the enzyme being ubiquitous, they also produce too varied effects.

That drugs were selective in their effects had been obvious from their first use, but it was not until 1899 that Paul Ehrlich began to develop new drugs scientifically in the laboratory (p. 18). In 1901 the principle of selective toxicity was first applied to agriculture, when it was shown that an oatfield could be cleared of the weed yellow charlock by a spray of copper sulphate (*4*).

Individual Variation

That individuals respond differently to drugs is a matter of everyday experience. Leaving out hypersensitivity phenomena and idiosyncrasy (p. 444) it is clear that though all respond differently, it is not so differently that effects and doses cannot be reasonably predicted. To any one drug there are a few who are naturally intolerant and who will show the expected pharmacological effect at very low dose, and there are a few who will only begin to show it at a very high dose. It is important to remember this, not only because of the danger to the intolerant individuals but because, before abandoning a drug as useless it is important to consider whether in fact an adequate dose has been given. In some cases it is necessary to go to the maximum tolerated dose, that is to increase the dose until toxic effects appear and then to reduce it slightly (Parkinsonism, epilepsy).

Drug Combinations

Drug combinations are sometimes useful, for if drugs with similar therapeutic, but differing toxic, effects are used there will be synergism of the therapeutic but not of the toxic effects so that, in theory at any rate, there is less likelihood of toxicity. The drug combinations used to treat, for example, pain or hypertension attempt to make use of this.

In general, drug combinations in which the ingredients are all in the same tablet or capsule may be viewed with suspicion unless they are very well tried (*e.g.* Codeine Compound Tablets) and especially if careful grading of effect is needed for they all suffer from an important defect, that the dose of one drug cannot be altered without altering that of the others. It is especially undesirable that substances such as adrenocortical hormones, whose dose is critical, should be mixed in tablets with other drugs.

THE INFLUENCE OF AGE, SEX, DISEASE AND PERSONALITY ON DRUG ACTION

Age. The very old and the very young are liable to be more sensitive to many drugs, probably largely because the equipment for disposing of them in the body is less efficient.

Unfortunately in infants doses cannot be calculated as a proportion of adult doses on the basis of either body weight or surface area. Neonates have relatively lower glomerular filtration and renal plasma flow than adults and are defective in the ability to form glucuronides in liver and kidney, a common metabolic path for drugs. It is also probable that a wide variety of enzyme reactions are less well developed (5). These deficiencies are enhanced in premature babies. Neonates may fail to deal effectively with vitamin K analogues, sulphafurazole, chloramphenicol, barbiturates, morphine and curare, and possibly many other drugs. Penicillin excretion is delayed, but this may be, if anything, a useful defect. Older children are more tolerant than adults of digitalis (6), but tolerance to atropine and morphine is probably normal although the contrary is sometimes stated.

In the aged all central nervous system depressants are especially liable to have greater effect than normal and some may cause confusional states, which is why atropine is often substituted for hyoscine in anæsthetic premedication.

Sex. There are no clinically important sex differences in drug action, but the subject is poorly documented. Women are said to be more liable to become excited by morphine than are men.

Disease. Examples of the modification of drug action by disease are legion. Hepatic and renal insufficiency often result in defective metabolism or excretion and it is necessary to be wary whenever using drugs in such cases. Clinically important examples include morphine in hepatic failure and streptomycin and potassium in renal failure. Other examples can be found throughout the book.

Patients with an abnormal respiratory centre (raised intracranial pressure, severe pulmonary insufficiency) are unduly sensitive to drugs which depress respiration (opiates, barbiturates). The respiratory depressant effect of both morphine and of barbiturates is first manifested by slowing of the rate and normal people compensate for this by breathing more deeply, but patients with severe emphysema cannot do this. Patients with raised intracranial pressure may be restless and it is important to avoid respiratory depression when using drugs to quieten them.

Other examples include:—

Asthmatic attacks may be precipitated by choline drugs or by histamine.

Patients with myocardial infarction are especially liable to develop cardiac arrhythmias with digitalis or sympathomimetic amines.

Porphyria is precipitated by barbiturates and sulphonal and possibly by sulphonamides.

Myasthenia gravis is made worse by quinine and myasthenics are very sensitive to competitive neuromuscular blocking agents (curare) and resistant to depolarising agents (decamethonium). Patients with either this disease or dystrophia myotonica are liable to develop respiratory failure under general anæsthesia.

Patients with hypopituitarism and hypothyroidism are intolerant of cerebral depressants.

In shock, drugs injected subcutaneously may not be absorbed owing to existing intense vasoconstriction and then, as this passes off, all doses previously given may be absorbed simultaneously with dire results. In both severe œdema and in shock drugs should be injected i.m. or i.v., not s.c.

Schizophrenics are often tolerant of drugs affecting the central nervous system and high doses may be needed.

Psychoneurotics sometimes show exaggerated responses, especially to sedatives, and stagger and fall about on the smallest doses.

Some patients with mental diseases show paradoxical responses to drugs which affect the autonomic nervous system (*e.g.* methacholine), but such responses are not predictable enough to be of diagnostic use.

Men with prostatic enlargement are liable to develop urinary retention with sympathomimetic, anticholine and ganglion-blocking drugs. Pyloric stenosis may be converted to an obstruction if gastric peristalsis is abolished by anticholine drugs.

Therapeutic doses of digitalis have no significant effect on a normal heart.

A patient in pain may become confused if given a hypnotic without an accompanying analgesic, for the pain keeps him awake when the drug is acting maximally.

Some drugs may be given in a chemical form unsuited to a particular occasion, *e.g.* sodium salicylate should not be used in cases of heart failure (aspirin would be better), and potassium salts are dangerous in renal failure.

It is impossible to list completely the possible important alterations of drug effect caused by disease. The examples given above should suffice to show that safety in using drugs lies in knowledge of both drug and disease.

Personality. Not enough is known to enable any generalisations of practical utility to be made, but there is no doubt that the response to drugs acting on the central nervous system is influenced by personality.

It is a commonplace that the response to alcohol is different and characteristic for some individuals and this is probably a personality difference. Pavlov noted that dogs of "excitatory" temperament might need eight times as much sedative as dogs of "inhibitory" temperament. Another prominent example is the response to placebo or dummy administration. It is also known that placebo-reactors are liable to respond atypically to other drugs (8) and that the response to a drug may vary with alterations in mental state (9).

THE UNWANTED EFFECTS OF DRUGS

In this book the terms toxic effect, unwanted effect and side-effect are often used synonymously because to differentiate between them in general discussion is tiresome and often pedantic. When it is said that a drug is relatively safe, what is meant is that the therapeutic dose is well below the toxic dose, see "chemotherapeutic index", p. 19.

Unwanted effects of drugs are very common indeed, but may not be recognised for what they are. Symptoms or signs, such as fever, rash or collapse due to a drug may be attributed to disease. Patients frequently take drugs for minor ailments and only come to a doctor when some unwanted effect occurs; such symptoms are rarely connected with the drug by the patients. In addition patients may take drugs without realising they are doing so, the quinine in tonic water was responsible in the following case:*

"I saw a 43-year-old man in consultation who had a 7-week history of tinnitus and hearing loss. He had consulted an otologist, who found bilateral diminution in hearing, and a neurologist, who suggested the diagnosis of bilateral angle meningioma. Because of the history of daily ingestion of seven to eight drinks per day he was sent for a medical evaluation prior to further workup for neurosurgery. The history of alcohol ingestion was correct, but his diet was in general adequate. After a physical examination, which was not remarkable except for the facts already noted, casual discussion brought out the fact that the drinks were always gin and tonic. Since I had seen cinchonism in the southwest Pacific, I thought it worth while to change the beverage to Tom Collins. Within 48 hours the symptoms had disappeared. A test dose of 300 mg of quinine brought a return of the tinnitus. Later, a test dose of 150 mg produced the same effect. Three weeks after the discontinuance of the quinine, audiogram showed restoration of hearing.

"While I have not obtained the exact formula of quinine water, I am informed that the Schweppes brand contains about 30 mg. per pint. The man was ingesting about 100 mg. daily. It is clear that it would take an enormous consumption to produce the symptoms in the normal adult."

---

* YOHALEM, S. B. (1953). *J. Amer. med. Ass.*, **153**, 1304.

Unwanted effects may be classified (*4*):—

Overdose: *a.* absolute; *b.* relative
Intolerance
Side-effects
Secondary effects
Idiosyncrasy
Hypersensitivity:

a. anaphylactic shock
b. asthma
c. urticaria and angioneurotic œdema, immediate or delayed
d. serum-sickness syndrome (arthralgia, lymphadenopathy, fever, plus *c* above)
e. thrombocytopenia
f. granulocytopenia and agranulocytosis
g. aplastic anæmia
h. hæmolysis
blood dyscrasias
i. rashes, non-urticarial
j. fever
k. polyarteritis nodosa
l. severe hæmatemesis provoked by aspirin, peripheral neuritis, "nephritis" and some other rare drug-induced phenomena are perhaps due to hypersensitivity.

Overdose

With overdose of a drug toxic effects occur in direct relation to the total amount of drug in the body. They may be:—

a. **Absolute,** due to an acute excess or to cumulation of the drug in the body.

b. **Relative,** due to an underlying abnormality in the patient. In renal failure a usual dose of any drug normally excreted by the kidney will cause abnormally high blood levels, *e.g.* ganglion blocking drugs. Patients who have an abnormally low serum potassium are abnormally sensitive to digitalis, and ordinary doses may produce toxic effects, which are reversed if potassium is given.

Intolerance

Intolerance to drugs may be defined as a lowered threshold to the normal pharmacological action of a drug. Individuals vary greatly in their susceptibility to drugs and those at one extreme of the normal distribution curve are intolerant of the drugs, those at the other, tolerant.

Side-effects

The term side-effects is sometimes restricted to therapeutically undesired but *unavoidable* effects, because they are normal pharmacological actions of the drugs. They may be extensions to an undesirable extreme of the therapeutic effect (*e.g.* drowsiness with phenobarbitone), or an effect which is never wanted (*e.g.* vomiting with digoxin). A side-effect on one occasion may be the desired effect on another; *e.g.* atropine is used in anæsthetic premedication to reduce bronchial and salivary secretion, but this can be a troublesome side-effect when atropine is given to Parkinsonian patients to reduce tremor. The hypotensive effects of ganglion-blocking drugs are inevitably accompanied by undesirable effects due to parasympathetic block.

Secondary Effects

Secondary effects are the indirect consequences of a primary drug action. The best examples are vitamin deficiency or superinfection which may occur in patients whose normal bowel flora has been altered by antibiotics. Possibly the Herxheimer reaction (probably due to products released by killed organisms, usually spirochætes) is another type of secondary effect.

Idiosyncrasy

Idiosyncrasy implies an inherent qualitatively abnormal reaction to a drug, probably due to genetic abnormality. Porphyria is an example and so is the hæmolytic anæmia caused in 10% of American negroes by the antimalarial, primaquine, which has been shown to be associated with a deficiency of a particular enzyme in their red cells. A similar enzyme deficiency seems to be responsible for the hæmolytic anæmia which certain people in the Mediterranean area develop if they eat fava beans. It is probable that some of the hæmolytic reactions to drugs (sulphonamides, PAS, phenacetin, nitrofurantoin, vitamin K analogues) are due to such enzyme defects which make the red cells of susceptible patients unusually liable to hæmolysis, but other hæmolytic reactions have an immunological basis. These rare examples show that at present idiosyncrasy is of greater scientific interest than clinical importance.

Hypersensitivity Reactions

Hypersensitivity reactions are mediated by an antigen-antibody reaction. They include those reactions to drugs in which clinical symptoms are the result of sensitisation to the drug. This requires previous exposure. If the drug is a protein it can act by itself as the antigen, otherwise the drug may combine with body protein to form an antigenic combination.

The symptoms which may occur in hypersensitivity reactions are very varied since antigen-antibody reactions can affect any system in the body. Some drugs are particularly likely to produce certain symptoms, *e.g.* purpura from apronal (Sedormid), or rashes from streptomycin, but the same drug may produce quite different symptoms in different hypersensitive patients, *e.g.* aspirin may cause a rash in one, asthma or anaphylactic shock in others. There are several types of hypersensitivity reactions:—

a. **Anaphylactic Shock** may occur when penicillin, horse serum and a huge variety of other drugs, is given to a patient sensitised to that drug. The combination of antigen with antibody in the cells is followed by peripheral vasodilation, probably due to liberation of histamine, with a severe fall in blood pressure, fainting and sometimes death. Anaphylactic shock usually occurs suddenly, in less than an hour after the drug, but within minutes if it has been given i.v. Treatment is urgent, 1 ml. of 1 : 1,000 adrenaline should be given s.c. and a substantial dose of an antihistaminic i.m. or i.v. Aminophylline is sometimes advocated for circulatory collapse and hydrocortisone should be given i.v. to suppress any further response to the antigen-antibody reaction. It is advised that any ward or other place where anaphylaxis may be expected should have all the drugs and tools necessary to deal with it in one convenient kit (5), for when they are needed there is little time to think and none to run about from place to place.

b. **Asthmatic Attacks.** The antigen-antibody reaction causes liberation of substances, including histamine, which cause contraction of smooth muscle. Stimulation of the bronchial musculature may result in an asthmatic attack which can be fatal. 0·25 to 1·0 ml. of 1 : 1,000 adrenaline, s.c., will usually cut short an attack, the other treatments for asthma (p. 257) are also effective.

c. **Urticarial Rashes and Angioneurotic Œdema.** These are probably the commonest type of hypersensitivity reaction to drugs. They are usually accompanied by intense itching. The eyelids, lips and face are usually most affected, œdema of the larynx is rare but may be fatal in the absence of tracheostomy. The itching œdematous lesions probably follow the liberation of histamine by antigen-antibody combination in the skin. Such reactions may be generalised, but frequently are worst in and around the area of administration of the drug. They respond to adrenaline, ephedrine, antihistaminics and adrenocortical steroids.

Anaphylactic shock, asthma and urticarial skin lesions may occur separately or in combinations of varying severity; they are usually accompanied by fever, general malaise, nausea and sometimes by vomiting.

d. **The Serum-sickness Syndrome** occurs about 1 to 3 weeks after administration. Treatment is by adrenocortical steroids, and as above for urticaria.

e. **Thrombocytopenic Purpura** due to drugs is not common except with apronal (Sedormid) which is deservedly obsolete, but it has been reported occasionally after a large number of drugs. Sedormid combines with the platelets and this combination acts as an antigen causing production of antibodies so that on subsequent administration of the drug the antibodies cause immediate massive destruction of platelets, which may cause fatal hæmorrhage. Adrenocortical steroids may be useful.

f. **Granulocytopenia,** sometimes leading to agranulocytosis, is a very serious, though rare, hypersensitivity reaction wihch may occur with many drugs, *e.g.* chloramphenicol, sulphonamides, thiourea derivatives. Amidopyrine is notorious in this respect and should never be used. Treatment of agranulocytosis involves both stopping the drug responsible and giving penicillin to treat or prevent infection. Bone marrow "stimulants" such as nucleotides are of no use. If the blood picture does not improve following withdrawal of the drugs adrenocortical hormones should be given in severe granulocytopenia and in all cases of agranulocytosis, but proof of their beneficial effect, if any, is naturally hard to get.

g. **Aplastic Anæmia.** Treatment is as for agranulocytosis, but blood transfusions will be required. Chloramphenicol is probably the most important drug causing this often fatal disease (*6*).

h. **Hæmolytic Reactions** to drugs may be examples of idiosyncrasy (p. 444), but probably more often are due to hypersensitivity reactions, the drug combining with red cells to make them antigenic. Most drugs have at one time or another been suspected of causing hæmolysis but the most notorious are probably quinidine, quinine, methoin and stibophen in addition to those listed under "idiosyncrasy". The drug should be withdrawn and the patient transfused if necessary. Adrenocortical steroids are used if hæmolysis is very severe.

i. **Non-urticarial Rashes** occur in great variety, frequently they are weeping exudative lesions. It is often difficult to be sure when a rash is due to drugs. Apart from stopping the responsible drug, treatment is non-specific; in severe cases adrenocortical steroids may be tried. Skin sensitisation to antibiotics may be very troublesome, especially amongst those who handle them.

j. **Fever.** Treatment is to stop the drug.

k. **Polyarteritis Nodosa** is sometimes caused by drugs, especially sulphonamides, and sometimes thiouracil. Adrenocortical steroids are used.

Tests for Hypersensitivity to Drugs

Unfortunately there are no satisfactory *in vitro* tests for drug hypersensitivity. Antibodies to drugs should theoretically be detectable in the serum of hypersensitive patients, but in practice this is rarely possible.

Repeated blood counts in patients taking drugs known to cause blood dyscrasia, especially agranulocytosis, appear at first sight to be desirable, but as the onset is ordinarily very sudden they commonly fail to give protection and may give a false sense of security. In addition spontaneous fluctuations in the number of granulocytes make the interpretation of such counts difficult, especially in children. Such routine blood counts are probably not worth doing. The best protection is to tell the patient to report at once any fever, enlarged glands or sore throat and to stop taking the drug until he has had advice. Unfortunately this can lead to frequent interference with therapy in nervous patients. Although innumerable drugs are capable of causing dyscrasias, troxidone, antithyroid drugs, phenylbutazone, methoin, gold, phenacemide and prolonged courses of sulphonamides are particularly notorious. A few drugs such as amidopyrine and phenazone have been abandoned because of the risk of blood dyscrasias, and courses of others, such as chloramphenicol, are kept short for this reason.

Test dosing can be very dangerous as a "test-dose" may be large enough to produce a fatal reaction in very hypersensitive patients. A patient has reacted to less than one unit of penicillin, another to 14 μg. of apronal (Sedormid). Another disadvantage is that test doses may give misleading results; a patient may not appear to be hypersensitive to a drug as judged by skin tests and yet react to a larger dose of it with, say, an asthmatic attack. If test dosing is performed then it should be started with minute amounts, and these slowly increased. Patch tests, intradermal or subcutaneous injections are usually used as the skin is easy to observe for a reaction, but patch tests are especially unreliable except in cases of sensitisation due to application to the skin. There is a variety of other techniques.

Desensitisation

Once a patient becomes hypersensitive to a drug, then it is better that he should never again come into contact with it. However, this can be inconvenient, for instance in hypersensitivity to antituberculous drugs in patients with tuberculosis, or in nurses. Such patients can be desensitised by giving very small amounts of allergen which are then gradually increased until a normal dose is tolerated. This may have to be done under cover of either an antihistaminic or of an adrenocortical steroid, or both, to prevent reactions during the desensitisation procedure. (Details of desensitisation to penicillin are given on p. 38, and to streptomycin and PAS on p. 67.) The mechanism underlying desensitisation is not understood but may involve the production by the patient of a different (blocking) antibody which competes successfully for the allergen but whose combination with it is innocuous. Sometimes hypersensitivity is to a part of the preparation other than the essential drug and merely changing the preparation is sufficient, *e.g.* some cases of fever from mercurial diuretics.

Prevention of Hypersensitivity Reactions is very important since they may be fatal. Patients should always be told when they are thought to be hypersensitive to a drug, and it is essential that if a patient says he is sensitive to some drug then that drug should *not* be given without careful testing. Assumption that patients are all either ignorant or stupid can cause deaths: A young man was admitted to hospital for an interval appendicectomy, but had a sore throat and slight fever. The house surgeon said this would soon clear up with penicillin, but the patient at once protested, saying that he was seriously sensitive to penicillin. The doctor said that in that case they would use another drug, but in fact gave the patient penicillin and he died from anaphylactic shock (*1*). The only way to completely prevent hypersensitivity reactions to drugs is to cease to use any drugs at all, but at least the unnecessary use of drugs for trivial complaints should be avoided.

Reactions to Intravenous Injections are fairly common, hypotension, renal pain, rigors and fever may occur, especially if the injection is very rapid. Some are due to foreign substances in the solutions and probably not to hypersensitivity.

GUIDE TO FURTHER READING

On General Pharmacology

(*1*) VELDSTRA, H. (1956). Synergism and potentiation. *Pharmacol. Rev.*, **8,** 339.

(*2*) HUNTER, F. E., and LOWRY, O. H. (1956). The effects of drugs on enzyme systems. *Pharmacol. Rev.*, **8,** 89.

(*3*) UNNA, K. *et al.* (1950). Dosage of drugs in infants and children. Atropine. *Pediatrics*, **6,** 197.

(*4*) ALBERT, A. (1960). Selective Toxicity. London: Methuen, 2nd ed.

(*5*) KRETCHMER, N. (1959). Practical therapeutic implications of immaturity. *Pediatrics*, **23,** 638.

(*6*) MATHIS, S. *et al.* (1952). Comparison of the tolerance of adults and children to digitoxin. *J. Amer. med. Ass.*, **150,** 191.

(*7*) DRAGSTEDT, C. (1958). Oral medication with preparations for prolonged action. *J. Amer. med. Ass.*, **168,** 1652.

(*8*) FELSINGER, J. M. VON, LASAGNA, L., and BEECHER, H. K. (1955). Drug-induced mood changes in man. Personality and reactions to drugs. *J. Amer. med. Ass.*, **157,** 1113.

(*9*) BEECHER, H. K. (1956). Evidence for increased effectiveness of placebos with increased stress. *Amer. J. Physiol.*, **187,** 163.

(*10*) KORNETSKY, C., and HUMPHRIES, O. (1957). Relationship between effects of a number of centrally acting drugs and personality. *Arch. Neurol. Psychiat. (Chicago)*, **77,** 325.

(*11*) FUHRMAN, F. A. (1946). The effect of body temperature on drug action. *Physiol. Rev.*, **26,** 247.
(*12*) SEEVERS, M. H., and WOODS, L. A. (1953). The phenomena of tolerance. *Amer. J. Med.*, **14,** 546.

On Unwanted Reactions to Drugs

(*1*) ALEXANDER, H. L. (1955). Reactions with Drug Therapy. Philadelphia: Saunders.
(*2*) MEYLER, L. (1958). Side effects of drugs. Amsterdam: Excerpta Medica Foundation.
(*3*) CARR, E. A. (1954). Drug allergy. *Pharmacol. Rev.*, **6,** 365.
(*4*) ROSENHEIM, M. L., and MOULTON, R., editors. (1958). Sensitivity Reactions to Drugs. Oxford: Blackwell.
(*5*) PRICKMAN, L. E., and LOFGREN, K. A. (1956). An emergency set to combat anaphylaxis. *J. Amer. med. Ass.*, **161,** 1159.
(*6*) SCOTT, J. L., CARTWRIGHT, G. E., and WINTROBE, M. M. (1959). Acquired aplastic anæmia: an analysis of 39 cases and review of the pertinent literature. *Medicine (Baltimore)*, **38,** 119.

APPENDIX A

WEIGHTS AND MEASURES

In this book all doses are given in the metric system. All new drugs are now prescribed metrically and there can be no doubt that it is both inevitable and desirable that this will become the sole system of dosage.

A table of the more important equivalents is given below. The British Pharmacopœia has sponsored "approximate equivalents". Under this system 1 grain is equivalent to 60 mg. The nearest figure is 65 mg. (actually 64·799). The use of 60 mg. as the equivalent leads to errors if multiples are used and so, for accuracy, the student should learn two equivalents. There is no good reason for not always using 65 mg. as the equivalent. A doctor's powers of performing mental arithmetic should be equal to it. In any case this is yet another reason for a change over to the metric system, when equivalents will no longer be a plague.

Mass

28 grams (G.) = 1 ounce
1 gram (G.) = 15 grains
65 milligrams (mg.) = 1 grain
(The "official" approximate equivalent is 60 mg., as explained above.)
1 kilogram (Kg.) = 2·2 pounds

Capacity

1 litre = 1·76 pints
28 millilitres (ml.) = 1 ounce
3·5 millilitres (ml.) = 1 fluid drachm
1·0 millilitres (ml.) = 17 minims

From the above, all equivalents likely to be needed in drug dosage can be calculated. Fuller tables should be unnecessary, for the doctor cannot constantly be consulting them and must learn to do simple conversions for himself. For domestic use the following are sufficiently accurate—

1 tablespoonful = 14 ml.
1 dessertspoonful = 7 ml.
1 teaspoonful = 3·5 ml.

but the sooner these measures become obsolete the better, although it will be a long time before measuring glasses become standard home equipment. In the meantime inaccurate dosage is the rule where domestic measures are used, although this often does not seem to matter much for the type of remedy given in this way.

PRESCRIBING

Prescriptions of pure drugs or preparations from the British National Formulary (B.N.F.) are satisfactory for almost all purposes. The composition of many of the preparations in the B.N.F. is laid down in either the British Pharmacopœia (B.P.) or British Pharmaceutical Codex (B.P.C.). Hence there is nowadays seldom any need to write a traditional prescription comprising base, adjuvant, corrective, flavouring and vehicle and the writing of such prescriptions is virtually dead.

It is both unnecessary and unwise to try to continue the use of traditional forms of prescription writing in Latin, for facility in their use can only be attained by frequent practice. To try to use these old-fashioned terms when they do not come naturally to the mind is to court the embarrassment of issuing an incomprehensible, or worse, an inaccurate, prescription.

It is both easier and safer to state the requirements in English. However, complete consistency is seldom to be achieved in any matter, and there is little doubt that certain convenient Latin abbreviations will survive for lack of English substitutes. These are chiefly used in hospital prescribing where instructions are given to nurses and not to patients for whom such abbreviations would be meaningless. They are listed at the end of this appendix. The elementary requirements of a prescription are that it should state *what* is to be given *to whom* and *by who prescribed*, and give instructions on *how much* should be taken *how often*, by what route and sometimes for *how long*, thus:—

1. **Date.**
2. **Address of Doctor.**
3. **Name and Address of Patient.**

4. R. This is a traditional esoteric symbol for the word "Recipe"—"take thou!", which is addressed to the pharmacist. It is pointless; but since many doctors gain a harmless pleasure from writing R with a flourish before the name of a proprietary preparation of whose exact nature they are quite ignorant, it is likely to survive as a sentimental link with the past.

5. **The Name and Dose of the Drug or Drugs.**

6. **Directions to the Pharmacist,** if any, thus—"mix", "make a solution". Write the total quantity to be dispensed if this is not stated in 5 above.

7. **Instructions for the Patient,** to be written on the container by the pharmacist. Here brevity, clarity and accuracy are especially important. It is dangerous to rely on the patient remembering verbal instructions.

8. **Signature of Doctor.**

It is no longer considered necessary to conceal from every patient the nature of his treatment. If the abbreviation n.p. (see below) is included in the labelling instructions, the pharmacist will write the proper name or contents of the medicine on the label. An additional advantage is that partly used medicines, given for symptoms such as pain or pruritus, will not accumulate anonymously, and therefore dangerously, in bathroom cupboards.

Examples of Prescriptions

For a patient with an annoying unproductive cough.

1, 2, 3 as above.
4. ℞.
5. Codeine Linctus, B.P.C., 4 ml.
6. Send 60 ml.
7. Label—Take 1 teaspoonful twice a day and on retiring. N.P.
8. Signature of doctor.

For a patient with Parkinsonism.

1, 2, 3 as above.
4. ℞.
5. Tincture of Stramonium, B.P., 0·5 ml.
   Hyoscine hydrobromide 0·5 mg.
   Water to 4 ml.
6. Mix and make a solution.
   Send 80 ml.
7. Label—Take 1 teaspoonful three times a day. N.P.
8. Signature of doctor.

The convenience of this prescription is that the dose can be increased gradually up to the limits of tolerance with perhaps greater convenience than with tablets. Confusion due to multiple tablets is avoided and if necessary other ingredients, *e.g.* pilocarpine to relieve dry mouth, may be added.

Dangerous Drugs Act

When a drug covered by the *Dangerous Drugs Act* (D.D.A.) is prescribed, *the name and address of the patient* and the *total amount* of the "dangerous drug" prescribed *must* be written on the prescription, also the doctor's *usual signature* and *address*. This is a *legal requirement*. However in the case of preparations in the B.P., B.P.C., and B.N.F. the total amount need not be stated.

The Dangerous Drugs Act covers broadly opium, morphine and synthetic morphine substitutes, cocaine and cannabis indica. Certain commonly used preparations containing small amounts of these drugs are exempt from the regulations, *e.g.*:—

Ipecacuanha and Opium Tablets (Tablets of Dover's Powder), B.P.
Squill Opiate Linctus (Gee's Linctus), B.P.C.
Kaolin and Morphine Mixture, B.P.C.

For details of the D.D.A., and for information about the various Schedules of Poisons, books on forensic medicine should be consulted.

Incompatibility in Prescribing

There are three types:—

1. **Therapeutic.** The desired effect of one ingredient is prevented by another.

2. **Pharmaceutical.** The preparation becomes disgusting or ingredients separate out.

3. **Chemical.** The ingredients react together chemically in an undesirable fashion. The classic example is the mixing of alkaloidal salts with alkali. At least one death has occurred from the precipitation of a strychnine salt by alkali so that the total amount of strychnine was consumed in the final dose taken from the bottle.

Doctors generally do not possess the knowledge of chemistry which would be required to avoid chemical and pharmaceutical incompatibilities. They therefore nowadays confine their extempore prescribing to well-trodden paths. Therapeutic incompatability is more of a theoretical than a practical risk.

Abbreviations

a.c., ante cibum	before food
b.d., bis in die	twice a day (b.i.d. is sometimes used)
i.m., intramuscular	by intramuscular injection
I.U.	International Unit
i.v., intravenous	by intravenous injection
n.p., nomen proprium	proper name
o.d., omni die	every day
o.m., omni mane	every morning
o.n., omni nocte	every night
p.c., post cibum	after food
p.o., per os	by mouth
p.r.n., pro re nata	as required. It is best to add the maximum frequency of repetition, *e.g.* Codeine Compound Tablets, 1 or 2 p.r.n., 4-hourly

q.d.s., quater in die sumendus	four times a day (q.i.d. and q.q.h. are sometimes used)
q.s., quantum sufficiat	a sufficiency, enough
rep., repetatur	let it be repeated, as in rep.mist(ura), repeat the mixture
s.c., subcutaneous	by subcutaneous injection
s.o.s., si opus sit	if necessary. It is useful to confine s.o.s. to prescriptions to be repeated once only and to use p.r.n. where many repetitions are intended
stat, statim	immediately
t.d.s., ter in die sumendus	three times a day (t.i.d. is sometimes used)

DRUG NAMES

Any drug may have names in both of the following classes:—

Non-proprietary Name.

a. Official name. The name used in an official pharmacopœia.

b. Approved name. The name given by the British Pharmacopœial Commission to a drug which is not included in the British Pharmacopœia.

Proprietary Name. The name is the property of a pharmaceutical firm which sells, although it may not have made, the drug.

If a non-proprietary name exists it should be used for the sake of clarity, for economy (sometimes), and because a pharmacist, confronted by a prescription, is obliged to supply that substance alone.

Thus, if cyanocobalamin is prescribed, any of the following "brands of cyanocobalamin" may be dispensed: Anacobin, Bitevan, Cytacon, Cytamen, Megalovel, Rubramin. But if, say, Cytamen is prescribed, of the above preparations only Cytamen will do, and if not in stock it must be sent for, with consequent delay. The physician should not rely on the pharmacist telephoning him to enquire if one of the other substances will serve. Anything which causes a pharmacist, nurse, or doctor to make a substitution opens the door to error.

The difficulties of nomenclature are well shown by the following. A dispenser "received a written slip from the theatre sister asking for 2 grams of procaine. Thinking procaine and Percaine to be similar substances, she used crystals from a bottle of Percaine and labelled the solution procaine. Giving evidence before the coroner she said that she had heard of Percaine but had never dealt with it in the pure drug form; she was so convinced that procaine and Percaine were identical that she did not consult any book." The patient into whom the drug was injected had severe convulsions in less than 15 minutes and died. In 1940 the *Lancet* expressed the hope that the manufacturers of Percaine would sell their product here under the name by which it was known in the United States: Nupercaine. The makers retorted, with some justice, that the trade mark Percaine was registered in 1918, whereas procaine was not adopted by the B.P. until 1932, so that it was for the B.P. to make a change if one was necessary. The B.P. Commission considered the matter "but it was not then thought possible to take any action." Later, in 1942, the makers of Percaine discarded this trade-name and substituted Nupercaine. Reporting this co-operative action, the *Lancet* added "it would be a blessing to both prescribers and dispensers of local anæsthetics if makers of procaine would relegate their brand names to second place and market their products as procaine (Smith) or procaine (Jones)." The necessity for some such system as this was emphasised in the following year when a woman died as a result of the newly named Nupercaine being confused with Novocaine (procaine). The proposed solution would, if generally applied, be a great relief to the medical profession. Unfortunately it is unacceptable to commercial pharmaceutical firms, although it is applied to insulin without apparent serious economic effect on the manufacturers. It is unlikely that the commonsense system of one name for one drug will be achieved in the near future as it seems to be impossible to reconcile uniformity with commercial enterprise at present.

In small centres the problem is often seen by doctors as less serious than it really is, for the local pharmacists know the practitioner's prescribing habits and stock all his favourite proprietary preparations.

Unfortunately the exhortation to use only non-proprietary names is very much a counsel of perfection, for many of these names are, as the advocates of proprietary names do not fail to point out, inconveniently cumbersome—*e.g.* bretylium tosylate (non-proprietary), Darenthin (proprietary); atropine methonitrate (non-proprietary), Eumydrin (proprietary). The search for proprietary names is a "major problem" for drug firms increasing, as they are, their output of new preparations. One well-known firm *averages* thirty new preparations a year, another warning of the urgent necessity for the doctor to cultivate eclecticism, which he can only do on a foundation of knowledge of drugs and criteria for their clinical assessment. The bleak outlook for practising doctors is shown by the following. One firm (in the U.S.A.) has "commissioned an I.B.M. machine to produce a dictionary of forty-two thousand nonsense words of an appropriate scientific look and sound." An official said "Thinking up names has been driving us cuckoo around here . . . proper chemical names are hopeless for trade purposes, of course. . . . We manufacture what are known as ethical drugs, sold on prescription. Doctors are the market we shoot for. A good trade name carries a lot of weight with doctors . . . they're more apt to write a prescription for a drug whose name is short, and easy to spell and pronounce, but has an impressive medical ring. . . . We believe there are enough brand new words in this dictionary to keep us going for years. . . . We don't yet know what proportion of names is unpronounceable . . . how many are obscene, either in English or in other languages and how many are objectionable on grounds of good taste: 'Godamycin' would be a mild example." The names which "look and sound medically seductive" are being picked out. "Words that survive scrutiny will go into a stock-pile and await the inexorable proliferation of new drugs."*

Perhaps the doctors have themselves to blame for this appalling prospect.

* *New Yorker*, July 14, 1956.

Guide to Further Reading on Drugs and the Law

(*1*) The Chemist and Druggist Poisons Guide, current edition. London: Chemist and Druggist.
(*2*) Glaister, J., and Rentoul, E. (1958). The control of the sale of poisons and dangerous drugs. *Brit. med. J.*, (*ii*), 1524.

APPENDIX B

DOSAGE OF ANTIMALARIAL DRUGS

(oral unless otherwise stated, and expressed as base)

For Suppression (also causal prophylaxis in the case of P. falciparum malaria): one of the following:—

chloroquine: 300 mg. once a week (a drug of first choice).
amodiaquine: 400 mg. once a week (a drug of first choice).
proguanil: 100 mg. daily.
pyrimethamine: 25 mg. once a week (a drug of first choice).
mepacrine: 100 mg. daily.
quinine: 650 mg. daily, if no other drug available.

For Treatment of Overt Attack: one of the following:—

chloroquine: 600 mg., then 300 mg. daily for 2 days (a drug of first choice).
amodiaquine: 600 mg., then 400 mg. daily for 2 days (a drug of first choice).
mepacrine: 300 mg. 3 times a day on first day.
300 mg. twice a day on second day.
100 mg. 3 times a day for five days.
quinine: 650 mg. 3 times a day for 7 days.

For Emergency Treatment: one of the following:—

chloroquine or amodiaquine: 200 to 300 mg. i.m. and repeated 6 hours later. Infusion i.v. is feasible (400 mg. in 500 ml. 0·9% sodium chloride over 1 hour) but liable to cause hypotension. (These are drugs of first choice.)
mepacrine: 300 mg. i.m. and repeated 6 hours later.
quinine dihydrochloride: 650 mg. i.v. at a rate not exceeding 65 mg. a minute, up to 3 times a day. Injection i.m. causes necrosis.

For Radical Cure: one of the following, combined with therapy for the overt attack:—

primaquine: 15 mg. daily for 14 days (first choice).
pentaquine: 10 mg. 3 times a day for 14 days.

Confusion sometimes arises when doses of antimalarials are expressed as being "of the base" or "of the salt", as this can lead to undertreatment, *e.g.* a 300 mg. tablet of amodiaquine hydrochloride contains 200 mg. of the base, *i.e.* the active antimalarial). Most tablets are expressed as "base" by their makers, as well as the weight of the salt, as there is more than one salt available of several antimalarials.

For children: for suppression, treatment of overt attack and radical cure:—

Under 1 year, $\frac{1}{8}$–$\frac{1}{5}$ adult dose
1– 3 years, $\frac{1}{6}$–$\frac{1}{3}$,, ,,
3– 6 years, $\frac{1}{5}$–$\frac{1}{2}$,, ,,
6– 9 years, $\frac{1}{2}$–$\frac{3}{4}$,, ,,
9–14 years, $\frac{3}{4}$,, ,,
over 14 years, adult dose

For emergency treatment, chloroquine 5 mg. Kg. i.m. and repeat after 24 hours.

APPENDIX C

SURGERY IN DIABETIC PATIENTS*

For interval surgery the patient should be admitted 3 days before operation so that the control of the diabetes can be adjusted according to the results of urine tests and blood sugar analyses. It is better not to give glucose solutions, or anything else, within 4 hours before operation as to do so increases the risk of vomiting during or after the anæsthetic.

There are three main groups of patients:—

1. diabetics who do not normally require insulin;
2. diabetics who are managed by diet and insulin and in whom there is no ketosis;
3. emergency cases with acute surgical lesions, infections or ketosis.

1. Diabetics Who Do Not Require Insulin

To compensate for bed rest, alter the diabetic diet to one containing 250 to 500 Calories less than the patient's usual diet. If glycosuria of over 0·75% persists or the blood sugar is high then treat as in paragraph 2.

Before Operation: No glucose by mouth and no insulin.

During Operation: No i.v. glucose and no insulin. For operations lasting more than about 1 hour treat as in paragraph 2.

After Operation: Manage as for a normal patient, but test urine for sugar and ketones every 3 hours in the day time. If there is persistent glycosuria or ketosis give soluble insulin half-an-hour before meals to control it.

2. Diabetics Who Normally Require Insulin

Routine Interval Surgery: Reduce the diet by 250 to 500 Calories and, 3 days before operation, transfer from the long-acting insulin to 3 approximately equal doses of soluble insulin half-an-hour before meals, the total daily dose of insulin being unaltered, *e.g.* change Insulin Zinc Suspension 72 I.U. daily to 3 doses of 24 I.U. of soluble insulin.

Before Operation: no glucose by mouth or i.v. Operations before 12 noon: the patient should have nothing to eat after the previous evening meal. Give the morning dose of soluble insulin s.c. immediately before the anæsthetic.

---

* This account is based on that written by Dr. A. G. Spencer for the University College Hospital Handbook, 1959.

Operations after 12 noon: the patient will usually be allowed a light breakfast and half the morning dose of soluble insulin should be given before this meal. Immediately before the anæsthetic give the remainder of the morning dose of soluble insulin.

DURING OPERATION: give 5% glucose i.v. at the rate of 1 litre 4 to 6 hours and soluble insulin, 20 I.U., s.c., per litre.

AFTER OPERATION: continue 5% glucose i.v. at the rate of 1 litre 4 to 6 hours and soluble insulin, 20 to 30 I.U., s.c. with each litre, according to urine sugar tests or blood sugar estimations. Include electrolytes and blood as required.

Commence the normal post-operative feeding régime, building up to the usual diabetic diet as soon as practicable. Give soluble insulin half-an-hour before meals according to the urine tests. Transfer to long-acting insulin when this is convenient.

3. Emergency Operations

DIABETIC KETOSIS. When a surgical emergency is complicated by diabetic ketosis an attempt should be made to control the ketosis before the operation. Management during the operation will be similar to that described in paragraph 2, except that more insulin may be necessary.

WHEN DIABETIC PATIENTS HAVE HAD THEIR MORNING INJECTION OF A LONG-ACTING INSULIN: Urine and blood sugar estimations are required before and after the operation. Give 5% glucose i.v. during and after the operation and soluble insulin according to the urine sugar and blood sugar tests and depending on the dose and type of long-acting insulin that has been given.

4. Minor Operations

For example, simple dental extractions and manipulations (for multiple extractions or when there is infection the patient should be admitted to hospital). A suitable soft post-operative diet of appropriate Calorie and carbohydrate content must be arranged. Plan the operation for between 12 noon and 5 p.m. Omit the usual dose of long-acting insulin on the morning of the operation and substitute soluble insulin, one-quarter of the usual total daily dose, before a light breakfast 6 hours preceding the operation. Take a light evening meal after the operation and soluble insulin, 10 to 30 I.U. s.c. according to the urine sugar tests. Return to the normal routine the next day.

GENERAL REFERENCES

The following are sources of further information on any chapter:—

Goodman, L. S., and Gilman, A. *The Pharmacological Basis of Therapeutics*, 2nd ed. New York: Macmillan, 1955.

Drill, V. A., editor. *Pharmacology in Medicine*, 2nd ed. New York: McGraw-Hill, 1958.

Sollmann, T. *A Manual of Pharmacology and its Application to Therapeutics and Toxicology*, 8th ed. Philadelphia: Saunders, 1957.

Modell, W., editor. *Drugs of Choice 1960–1961*. St. Louis: Mosby, 1960. This book is published biennially.

Osol, A. and Farrar, G. E. *The Dispensatory of The United States of America*, 25th ed. Philadelphia: Lippincott, 1955. Perhaps the biggest compendium of information on drugs in existence.

Beckman, H. *The Year Book of Drug Therapy*. Chicago: Year Book Publishers. Published annually. Contains abstracts of original papers from many journals.

Martindale. *The Extra Pharmacopoeia*, 2 vols., 24th ed. London: Pharmaceutical Press, 1958. An encyclopædia.

Robson, J. M., and Keele, C. A. *Recent Advances in Pharmacology*, 2nd ed. London: Churchill, 1956.

New and Non-official Drugs. Philadelphia: Lippincott. This book is published annually and contains descriptions of drugs "evaluated by the council on drugs of the American Medical Association".

Clinical Pharmacology and Therapeutics is the official bimonthly publication of the American Therapeutic Society. It was published for the first time in January 1960.

Pharmacological Reviews is published quarterly. It contains definitive reviews on specialised topics.

British Journal of Pharmacology and Chemotherapy is published quarterly. It specialises in laboratory work, largely on animals.

Journal of Pharmacology and Experimental Therapeutics is published monthly. It specialises in laboratory work, largely on animals.

INDEX

For convenience of reference a number of proprietary names are included and are followed by the non-proprietary name. For the sake of brevity the various salts (e.g. chloride, tartrate, etc.) of the drugs listed are omitted except where differences are especially important. Where there are many references to a drug the major discussion is indicated by the use of heavy type.

Abbreviations, 453-454
Abortion, 358
Acacia, 318
Acepromazine, 206
Acetamidophenol, 173
Acetanilide, 173
Acetarsol, 71, 80
Acetates, 215
Acetazolamide, 309-310
Acetomenaphthone, 340
Acetophenetedin, 173
Acetylcholine, 231-232. *See also* Choline drugs
  antagonists, 239
  at neuromuscular junction, 135
Acetylcholinesterase. *See* Cholinesterase
Acetylsalicylic acid. *See* Aspirin
Acetylstrophanthin, 289, 291
Achalasia, 263-264
Achlorhydria, 330
ACHROMYCIN: tetracycline
Acne, 428
Aconite, 420
ACTH. *See* Corticotrophin
ACTHAR: corticotrophin
Actinomycosis, 72, 368
ADALIN: carbromal
ADAPRIN: acetomenaphthone
ADCORTYL: triamcinolone
ADCORTYL-A: triamcinolone acetonide
Addiction, 183-197
  to alcohol, 194-195
  to amphetamine, 208
  to cocaine, 144-145
  to heroin, 164-165
  to hypnotics and sedatives, 109
  to morphine, 160-161
  to opium, 160
Addisonian crisis, 96
Addison's disease, 95-96
Addison's disease—*continued*
  corticotrophin test for, 89-90
  history, 87
Adrenal virilism, 98
ADRENALIN: adrenaline
Adrenaline, 249-253. *See also* Sympathomimetics
  blood sugar and, 379
  uses, anaphylaxis, 445
    asthma, 257-258
    hæmostatic, 339
    urticaria, 445
Adrenergic blocking drugs, 266-268
  in hypertension, 260
Adrenochrome, 212
Adrenocortical insufficiency, 95-96
  anæsthesia and, 149
  in severe illness, 98
Adrenocortical steroids, 87-100
  choice of, 93-94
  contra-indications, 94
  dose, 94-95
  history, 87
  insufficiency, 95-96
  insulin and, 379
  peptic ulcer and, 317
  toxic effects, 94
  uses, 95, 99-100
    alcoholism, 194
    arthritis, 176-178
    asthma, 257-258
    desensitisation, 447
    gout, 180
    hypersensitivity, 445-446
    hypotension, 260
    leukæmia, 412, 414
    myotonia, 78
    penicillin sensitivity, 38
    rheumatic fever, 175
    staphylococcal infections, 54
    tuberculosis, 68
    typhoid, 45

Adrenocortical steroids—*continued*
  uses, ulcerative colitis, 327–328
  withdrawal, 97–98
Adrenocorticotrophic hormone. *See* Corticotrophin
Adrenogenital syndrome, 98
  corticotrophin test in, 89
Adrenolytics, 266. *See* Adrenergic blocking drugs
ADRESON: Cortisone acetate
Adsorbents, 326–327
AEROSPORIN: polymyxin B
Agar, 319, 320
Age and drugs, 440
Aggression, 211
Agranulocytosis, 21, 446
ALBAMYCIN: novobiocin
ALBUCID: sulphacetamide
Albumen, 304
Alcohol, ethyl, 188–197
  methyl, 196–197
  toxicity, 193–195
    nikethamide in, 223
    aneurine in, 401–402
  uses, 192, 196
    angina, 265
    methanol poisoning, 197
    psychoneurosis, 271
    vasodilator, 269
Alcoholic drinks, 195–196
ALCOPAR: bephenium
ALDACTONE: spironolactone
Aldosterone, 93, 313
  antagonists, 313
ALEUDRINE: isoprenaline
ALEVAIRE: 216
ALFICETYN: chloramphenicol
Alkalosis, 316–317
Allergic states. *See also* Hypersensitivity and Asthma
  histamine and, 333
  rhinitis, 253, 256, 334
Aloes, 323
Alopecia, 428
Aloxidone, 112
Alphaprodine, 166
ALTAFUR: furaltadone
Aluminium acetate lotion, 416
Aluminium hydroxide, 315, 316, 317
Aluminium paste, 419
Aluminium silicate. *See* Kaolin
Amanita, muscaria, 233, 234
  phalloides, 234
AMBISTRYN: streptoduocin
AMECHOL: methacholine
Amethocaine, 143, 145. *See also* Local analgesics
Amethopterin, 413, 414
Amidopyrine, 174
Amine oxidase inhibitors, 209–210
***p*-Aminobenzoic acid,** 31, 399, 423
Aminometradine, 311
Aminophylline, 225–227
  uses, anaphylaxis, 445
    asthma, 257–258
    chronic bronchitis, 258
    heart failure, 292
    vasodilator, 269
Aminopterin, 413
Amino-uracil diuretics, 311
Amiphenazole, 224
Amisometradine, 311
Ammoidin, 427
Ammonia, aromatic solution, 224
  and ipecacuanha mixture, 216
Ammoniated mercury ointment, 420
  and coal tar, 418, 426
Ammonium chloride, mercurials with, 306
  uses, diuretic, 310–311
    expectorant, 215
Amodiaquine, 76–77
  dose, 457–458
Amœbiasis, 72–73
AMPHAMED: amphetamine
Amphetamine, 207–209, 255. *See also* Sympathomimetics, Antidepressants
  uses in, barbiturate poisoning, 110
    epilepsy, 114, 115
    hiccough, 205
    mental disorder, 210–211
    migraine, 156
    Parkinsonism, 247
Amphotericin, 51
Amyl nitrite, 263. *See also* Nitrites
Amylobarbitone, 104. *See also* Barbiturates
Amylocaine, 146
AMYTAL: amylobarbitone
Anabolic agents, 359
ANACARDONE: nikethamide
Anæmia, 385–396
  Addisonian, 392
    iron in, 387

Anæmia—*continued*
  aplastic, 446
  hæmolytic, 444, 446
  iron deficiency, 386
  pernicious, 392
    iron in, 387
Anæsthetics, 121–150
  history, 121–122
  hypotension in, 273
  in adrenocortical deficiency, 149
  in cardiac disease, 148
  in children, 150
  in diabetes, 149
  in liver disease, 148
  in muscle disease, 149
  in obstetrics, 147
  in old age, 149–150
  in porphyria, 149
  in renal disease, 148
  in respiratory infection, 148
  in thyroid disease, 149
  local. *See* Local analgesics
  mode of action, 122
  premedication, 124–126
  stages, 122
Analeptics, 222–224
  uses in alcohol poisoning, 194
    in barbiturate poisoning, 109–110
Analgesics, 151–181
  choice of, 153–156
  local. *See* Local analgesics
  obstetric, 146–147
  trials of, 152–153
Anaphylactic shock, 445
ANCOLAN: meclozine
Androgens, 353–354
  and the skin, 423
ANDROSTALONE: methylandrostanolone
ANECTINE: suxamethonium
Aneurine, 400–402. *See also* Vitamin B
  in alcoholism, 194
Angina pectoris, 265–266
  nitrate and nitrites in, 262–264
  xanthines in, 225, 226
Angioneurotic œdema, 333, 445
ANGISED: glyceryl trinitrate
Anileridine, 166
Aniline derivatives, 173
Anion-exchange resins, 312
Anise, 318
Ankylosing spondylitis, 178
Ankylostoma, 85
Anorexia nervosa, 376
ANSOLYSEN: pentolinium
ANTABUSE: disulfiram
Antacids, 315–317
Antagonism, 438
ANTEPAR: piperazine
Anterior pituitary. *See* individual hormones
Anthelminthics, 83–86
ANTHISAN: mepyramine
Anthracenes, 322–323
Anthrax, 83
Antibiotic, 20–21. *See also* Antimicrobials
Anticholines, 239–248
  uses, 244–245
    anti-emetic, 218, 219, 220
    asthma, 257
    diarrhœa, 327
    peptic ulcer, 317–318
Anticholinesterases, 229, **234–239**
  neuromuscular block and, 135, 136
Anticoagulants, 341–350
  choice of, 346
  contra-indications, 349
  indications, 346–348
  long term, 348–349
  surgery and, 349–350
  toxicity of, 342, 345
Anticonvulsants, 110–116
Antidepressants, 200–204, 207–210
Antidiuretic hormone, 352–353
ANTIDOL: salicylamide
Anti-emetics, 217–222
Anti-epileptics, 110–116
ANTIFEBRIN. *See* Acetanilide
Antihæmophilic globulin, 338
Antihistaminics, 332–335
  as histamine liberators, 330
  uses, 333–334
    anti-emetic, 218, 219, 220
    antipruritic, 421
    asthma, 257
    cough, 216
    hypersensitivity reactions, 38, 67–68, 445, 447
    Parkinsonism, 247
    skin diseases, 425, 426
Antimalarials, 74–78
  dosage, 457–458
Antimetabolites, 410, 412–413

Antimicrobials, 18 86. *See also* individual drugs
  antagonism between, 26–27
  bacteriostatic, bactericidal, 21, 27
  combinations, 26-27
  definition, classification, 20-21
  history, 18-20
  nutritional deficiency, 28
  principles of use, 29-30
  resistance to, 24-26
  use and choice, 21-24
    in prophylaxis, 28-29
    in skin diseases, 425, 426
Antimitotics, 409
Antimony, 82
  in schistosomiasis, 83
  poisoning, 431
Antimonylgluconate, 82
Anti-pruritics, 421
Antipyretic analgesics, 167–174
ANTIPYRIN, 173
Antiseptics, 419–420
  ointments, 420
Antitetanus serum, 117
Antithyroid drugs, 367–374
  and the fœtus, 148
  in exophthalmos, 365
Antitussives, 214–217
ANTOXYLIN(S): gonadotrophin, chorionic
ANTRENYL: oxyphenonium
ANTRYPOL: suramin
ANTUITRIN-S: gonadotrophin, chorionic
ANTURAN: sulphinpyrazone
Anxiety states, 211
A.P.C. tablets, 171
Aperient. *See* Purgative
Aphthous ulcers, 100
Aplastic anæmia, 446
Apomorphine, 221, 298
APRESOLINE: hydralazine
APRINOX: bendrofluazide
Apronal, 108
AQUAVIRON: testosterone
ARALEN: chloroquine
ARAMINE: metaraminol
Arecoline, 233
ARFONAD: trimetaphan
ARISTAMIDE: sulphasomidine
Aromatic diamidines, 81
Arrhythmias, 298–303
Arsenic, 80–81
Arsenic—*continued*
  history, 19
  poisoning, 431
Arsphenamines, 80. *See also* Arsenic
ARTANE: benzhexol
Arterenol. *See* Noradrenaline
Arterial thrombosis, 348
Arthritis, 176–178
ASCABIOL: benzyl benzoate
Ascariasis, 84
Ascorbic acid, 403–405
  folic acid and, 394
  iron and, 386
Aspirin, 170–171. *See also* Salicylates
  compound tablets, 171
  phenacetin and, 171
ASPRO: aspirin
Asthma, 257–258
  adrenaline in, 253
  amyl nitrite in, 263
  antihistaminics in, 334
  due to drugs, 445
  ephedrine in, 254
  ethylnoradrenaline in, 254
  isoprenaline in, 254
  methoxyphenamine in, 255
  theophylline in, 225–226
A.T.10: dihydrotachysterol
Ataractic, 101
ATARAX: hydroxyzine
Atebrin. *See* Mepacrine
ATEMPOL: methylpentynol
Atrial fibrillation, 300–301
Atrial flutter, 301
Atropine, 239–242. *See also* Anticholines
  poisoning, 241–242
  uses, anticholinesterase poisoning. 235
    heart-block, 302
    morphine with, 159
    "mushroom" poisoning, 233–234
    myasthenia, 238
    neostigmine with, in neuromuscular block, 137–138
    Parkinsonism, 247
    premedication, 125
Atropine methonitrate, 242
  in whooping cough, 57, 216
AUREOMYCIN: chlortetracycline
Auricular fibrillation, 300–301
Auricular flutter, 301
Aurothiomalate, 177

AVERTIN: bromethol
AVLOCLOR: chloroquine
AVLOSULFON: dapsone
AVOMINE: promethazine chlorotheophyllinate
Azacyclonol, 207. *See also* Tranquillisers
AZULFIDINE: sulphasalazine

Bacillary dysentery, 61
Bacitracin, 48
  uses, skin infections, 422
    staphylococcal infections, 54
Bacterial endocarditis, 59-60
Bacterial resistance, 24–26
B.A.L., 431
Baldness, 428
BANOCIDE: diethylcarbamazine
BANTHINE: methantheline
BARATOL: trimethidinium
Barbitone, 103, 104. *See also* Barbiturates
Barbiturates, 103–105
  addiction, 186
  poisoning, 109
  uses, 108
    anæsthetic, 132–133
    epilepsy, 111–116
    hepatic failure, 160
    hypertension, 281
    local analgesic poisoning, 142
    mental disorder, 210–211
    obstetric, 147
    pain, 151, 152, 155
    premedication, 125
    strychnine poisoning, 222
    tetanus, 119
Barrier cream, 417–418
Basal narcosis, 125–126
BECANTYL: 215
Bee stings, 418–419
Belladonna, 239, 242–243
Bemegride, 223–224
  in barbiturate poisoning, 110
Benactyzine, 207
BENADRYL: diphenhydramine
BENAPEN: benethamine penicillin
Bendrofluazide, 308
BENEMID: probenecid
Benethamine penicillin, 40
BENTONYL: triethanolamine trinitrate
BENTYL: dicyclomine
Benzathine penicillin, 40. *See also* Penicillin
Benzazoline. *See* Tolazoline
Benzchlorpropamide, 112
BENZEDREX: propylhexedrine
BENZEDRINE: amphetamine
Benzhexol, 246–247
Benzocaine, 146
Benzoic acid, 425
Benzoin inhalation, 214, 216
Benzonatate, 215
Benzpyrinium, 236. *See also* Choline drugs
BENZTRONE: œstradiol monobenzoate
Benztropine, 246–247
Benzyl benzoate, 426
Benzylpenicillin, 40, 41. *See also* Penicillin.
Bephenium, 85
Beri-beri, 400–401
Betel, 233
Bethanechol, 232. *See also* Choline drugs
Bezold-Jarish effect, 278
Bile acid, 319
Bile salts, 318–319
Biliary colic. *See* Colic
BIOSERPINE: reserpine
BIOTEXIN: novobiocin
Biotin, 399
Bisacodyl, 319, 323. *See also* Purgatives
Bismuth salts, 316
  in syphilis, 70–71
Bismuth sodium thioglycollate, 78
Bismuth subgallate, 326
Bites, 418–419
Bitters, 318
Blaud's pill, 388
Blepharitis, 68–69, 425
Blood coagulation, 337
Boils, 425
BONAMINE: meclozine
Boric acid, 419
BRADOSOL: domiphen
Bran, 319, 320, 325
Breast carcinoma, 357
Bretylium, 269–270, 281
BREVIDIL M: suxamethonium
British Anti-Lewisite, 431
Bromethol, 131. *See also* Basal narcotics

Bromethol—*continued*
  in tetanus, 119
Bromide, 105–107, 113
BROMURAL: bromvaletone
Bromvaletone, 107
Bronchial asthma. *See* Asthma
Bronchial carcinoma, mustine in, 410
Bronchiectasis, 57
  penicillin inhalations, 41
Bronchitis, 57
Bronchopneumonia, 58
Bronchospasm, amyl nitrite in, 263
BROXIL, 36
Brucellosis, 72
BUCROL: carbutamide
Buclizine, 219
Buffered cream, 417
BUSCOPAN: hyoscine butylbromide
Busulphan, 412, 414
Butacaine, 146
BUTANEFRINE: ethylnoradrenaline
BUTAZOLIDIN: phenylbutazone
Buthalitone, 133
Butobarbitone, 104, 105. *See also* Barbiturates

CAFERGOT, 156
Caffeine, 224–227
  uses, barbiturate poisoning, 109
    headache, 155
    migraine, 156
CAFRON: benactyzine
Calamine lotion, 417
Calciferol, 406. *See also* Vitamin D
CALCIPEN-V: phenoxymethylpenicillin
Calcium, 405–408
  blood coagulation and, 337
  digitalis and, 285
Calcium aminosalicylate, 64
Calcium carbonate, 316
Calcium chloride, 302
CALCIUM DISODIUM VERSENATE: sodium calciumedetate
Calcium gluconate, 408
Calcium hydroxide, 316
Calcium lactate, 408
Calomel, 323–324
CALPOL: paracetamol
CAMOQUIN: amodiaquine
Camphor, 224
  antipruritic, 421

Camphor—*continued*
  liniment, 420
Cannabis indica, 412
Cantharides, 420
CAPROKOL: hexylresorcinol
Caramiphen, 246–247
Carbachol, 232. *See also* Choline drugs
Carbamylcholine. *See* Carbachol
Carbasone, 80
  in amœbiasis, 73
Carbetapentane, 215
Carbimazole, 370. *See also* Antithyroids
Carbomycin, 50
Carbon dioxide, uses, expectorant, 215–216
    hiccough, 205
    tetany, 408
Carbonic anhydrase, 309
Carboxymethylcellulose, 320
CARBRITAL, 107
Carbromal, 107
Carbuncles, 425
Carbutamide, 383–384
Carcinoma, androgens in, 354
  breast, 357
  prostate, 357
Cardamom, tincture, 6
Cardiac arrest, 302–303
Cardiac arrhythmias, 298–303
Cardiac failure, 292–293
CARDIAZOL: leptazol
CARDOPHYLIN: aminophylline
Carminatives, 318
Carotene, 399
Cascara, 319, 323, 324, 325
Castellani's paint, 425
Castor oil, 319, 322, 325
Cathartic. *See* Purgative
CATHOMYCIN: novobiocin
Cation-exchange resins, 311–312, 331. *See also* Diuretics
Causalgia, 154, 268, 275
Caustics, 418
CAVODIL: pheniprazine
C.B. 1348, 411, 414
CEDILANID: lanatoside C *or* deslanoside
CENTRAZOL: leptazol
Cerebral thrombosis, 348
CETAVLON: cetrimide
Cetrimide, 419–420, 425, 427

CEVANOL: benactyzine
Chalk, 327
  and opium mixture, 157
Chancroid, 71
Charcoal, 318
Chelating agents, 431–432
Chemoprophylaxis, 28–29
Chemotherapeutic index, 19
Chemotherapy, 18–86. *See also* Antimicrobials, individual drugs and diseases
Cheyne-Stokes respiration, 225
Chickenpox, 22
Chilblains, 268
Chloral, 102
  addiction, 186
  uses, 108
    hepatic failure, 160
    obstetric, 147
Chloralformamide, 102
Chlorambucil, 411, 414
Chloramphenicol, 43–45
  uses, cholera, 74
    eye infections, 68
    meningitis, 60
    skin infections, 422
    staphylococcal infections, 54
    whooping cough, 57
Chlorbutol, 102, 220
Chlorcyclizine, 335. *See also* Antihistaminics
  as anti-emetic, 219
CHLORETONE: chlorbutol
Chlorhydroxyquinolines, 422, 425–426
Chlorisondamine, 274
Chlormerodrin, 307
Chlorodyne, 162, 327
Chloroform, 130. *See also* Anæsthetics
  and morphine, 162, 327
CHLOROMYCETIN: chloramphenicol
Chloroquine, 76–77
  dosage, 457–458
  uses, amœbiasis, 73
    arthritis, 177
    lupus erythematosus, 427
    sun-burn, 423
Chlorothiazide, 308. *See also* Diuretics
  uses, bromism, 106
    hypertension, 281
Chlorotrianisene, 355
Chlorpheniramine, 335. *See also* Antihistaminics
Chlorpromazine, 204–206. *See also* Tranquillisers
  uses, anæsthesia, 124
    anti-emetic, 218–220
    epilepsy, 114
    mental disorder, 210
    pain, 154–155
    Parkinsonism, 247
    premedication, 125
    pruritus, 421
    tetanus, 119
Chlorpropamide, 383–384
Chlortetracyline, 46–47. *See also* Tetracyclines
Chlorxylenol, 420
Cholecalciferol, 406. *See also* Vitamin D
Cholecystitis, 61
CHOLEDYL: choline theophyllinate
Cholera, 74
Cholesterol, reduction of blood, 357
Choline, 399
Choline drugs, 228–239
  classification, 229
  quinidine and, 294
  uses, 239
    expectorant, 216
    paralytic ileus, 326
    tachycardia, 299–300
    vasodilator, 265
Choline esters, 229, 231–233, 239
Choline theophyllinate, 226, 257
Cholinergic drugs. *See* Choline drugs
Cholinesterase inhibitors. *See* Anticholinesterases
Cholinesterases, 234
Chorionic gonadotrophins, 351
Christmas factor, 338
Chronic bronchitis, 57, 258
CIBAZOL: sulphathiazole
Cinchocaine, 143, 145. *See also* Local analgesics
Cinchonism, 79
Cinchophen, 179
Cirrhosis, choline in, 399
Citrate, 337
Citrovorum factor. *See* Folinic acid
Claudication. *See* Peripheral vascular disease
Climacteric symptoms, 356

Clinical trials, 11–16
CLOPANE: cyclopentamine
Coal tar, 418
COBADEX: hydrocortisone
Cobalt, 390
Cobra venom, 156
Cocaine, 143, 144–145. *See also* Local analgesics
  history, 140
Cocoa, 225, 227
Codeine, 163. *See also* Opiates
  compound tablets, 163
  uses, antitussive, 215, 216
    diarrhœa, 327
    obstetric, 147
CODELCORTONE: prednisolone
Coffee, 225, 227
COGENTIN: benztropine
Cola, 225, 227
COLCEMID: demecolcine
Colchicine, 178–179, 180–181
Colds, 256, 334
Colic, 154
  ganglion-blockers in, 275
  nitrites in, 263
Colitis, ulcerative, 327–328
COLLIRON, 388
COLLIRON I.V.: saccharated iron oxide
Collodion, 419
Colocynth, 323
Colonic surgery, 61
Coma, 430
COMBISTREP: streptoduocin
Common cold, 256, 334
COMPAZINE: prochlorperazine
Competitive block, 135, 136–138
Competitive inhibition, 438
Congestive cardiac failure, 292–293
Conjunctivitis, 68–69
Constipation, 324–326
Contraceptives, 358
Contrast media, 368–369
Convulsants. *See* Analeptics
Copper, deficiency, 390
  poisoning, 432
CORAMINE: nikethamide
COREDIOL: nikethamide
Corns, 418
Coronary artery disease. *See* Angina
Coronary insufficiency, 348
Coronary thrombosis, 346–347
CORTEF: hydrocortisone
CORTELAN: cortisone acetate
Corticosteroids. *See* Adrenocortical steroids
Corticotrophin, 88–91
  in ulcerative colitis, 327–328
Cortisol. *See* Hydrocortisone
Cortisone, 91–93. *See also* Adrenocortical hormones
  in vitamin D poisoning, 407
CORTISTAB: cortisone acetate
CORTISYL: cortisone acetate
CORTRIL: hydrocortisone
CORVOTONE: niketamide
COSCOPIN: noscapine
Cosmetics, 418
Cough, 214–217
COUMADIN: warfarin
Coumarins, 343–346. *See also* Anticoagulants
Counter-irritants, 420
Cramp, quinine in, 78
Creams, 417
CREMODIAZINE: sulphadiazine
CREMOMERAZINE: sulphamerazine
CREMOSUXIDINE: succinylsulphathiazole
CREMOTHALIDINE: phthalylsulphathiazole
Creosotes, 215
Cretinism, 366
CRONETAL: disulfiram
Crotamiton, 421
Croton oil, 323
Cryptorchidism, 351
CRYSTAPEN: penicillin
CRYSTAPEN V: phenoxymethylpenicillin
CRYSTOIDS: hexylresorcinol
Cumulation, 437
Curare. *See* Tubocurarine
Cushing's syndrome, corticotrophin test in, 89
Cyanide, poisoning, 432
Cyanocobalamin, 391–394
  in herpes zoster, 155
Cyanocobalamin peptide, 391
Cyclizine, 219. *See also* Anti-emetics
Cyclobarbitone, 104. *See also* Barbiturates
CYCLONAL: hexobarbitone
Cyclopentamine, 256

Cyclopropane, 130. *See also* Anæsthetics
  addiction, 186
Cycloserine, 50, 66
Cycrimine, 246–247
CYTAMEN: cyanocobalamin
Cytotoxic drugs, 409, 410–412

Dakin's solution, 419, 425
Dandruff, 427
Dangerous Drugs Act, 452–453
Dapsone, 82–83, 428
DAPTAZOLE: amiphenazole
DARANIDE: dichlorphenamide
DARAPRIM: pyrimethamine
DARENTHIN: bretylium
DARTALAN: thiopropazate
DBI, 384
DCA. *See* Deoxycortone
DDS, 82–83
DDT, 426
DECADRON: dexamethasone
Decamethonium, 138. *See also* Neuromuscular blocking agents
DECORTACETE: deoxycorticosterone
DECORTISYL: prednisone
7-dehydrocholesterol, 406
Dehydrocholic acid, 319
DELTA-CORTEF: prednisolone
DELTA-CORTELAN: prednisone acetate
DELTACORTONE: prednisone
DELTA CORTRIL: prednisolone
DELTA-EF-CORTELAN: prednisolone acetate
DELTA-STAB: prednisolone
DELYSID: lysergic acid diethylamide
Demecolcine, 178–179
Demerol. *See* Pethidine
Demethylchlortetracycline, 47
Demulcents, 318
Deoxycorticosterone. *See* Deoxycortone
Deoxycortone, 93. *See also* Adrenocortical hormones
Dependence, 183–184
DEPHADREN: dexamphetamine
Depolarisation block, 135–136
Depression, drugs in, 210. *See also* Antidepressants
Dermatitis, 416–428
Dermatitis herpetiformis, 428
Dermatomyositis, 99
Desensitisation, 447–448
Deserpidine, 277
Deslanoside, 289
Desoxycorticosterone. *See* Deoxycortone
Detergents, 216, 428
DEVEGAN: acetarsol
DEXA-CORTISYL: dexamethasone acetate
DEXAMED: dexamphetamine
Dexamethasone, 92, 93. *See also* Adrenocortical hormones
Dexamphetamine, 207–209. *See also* Sympathomimetics
DEXEDRINE: dexamphetamine
DEXTELAN: dexamethasone
Dextran sulphate, 342
Dextro-amphetamine. *See* Dexamphetamine
Dextromethorphan, 166
Dextromoramide, 166
Dextrose, 313
DEXULATE: dextran sulphate
D.F. 118: dihydrocodeine
DFP, 236
  poisoning, 234–235
Diabetes insipidus, 352–353
Diabetes mellitus, 375–384
  cortisone in, 96
  ketosis, 381–383
  oral drugs, 383–384
  surgery in, 459–460
DIABINESE: chlorpropamide
DI-ADRESON-F: prednisolone
DIAL: allobarbitone
di-amine oxidase, 332
Diamorphine, 164–165
DIAMOX: acetazolamide
DIANABOL: methandrostenolone
DIAPHYLLIN: aminophylline
Diarrhœa, 326–328
Diastase, 318
Dibenyline, 267
DIBENZYLINE: phenoxybenzamine
DIBOTIN: phenformin
DIBULINE: dibutoline
Dibutoline, 244
Dibutyl phthalate, 418
Dichlorphenamide, 310
DICODID: hydrocodone
Dicophane, 426

Dicoumarol, 343, 344. *See also* Anticoagulants
Dicyclomine, 244
Dienœstrol, 355
Diethazine, 246–247
Diethylcarbamazine, 84, 86
Digitalin, 289
Digitaline, 289
DIGITALINE (NATIVELLE'S CRYSTALLISED): digitoxin
Digitalis, 284–293
  administration, 290–291
  for children, 291
  effects, 285–288
  metabolism, 288
  preparations, 288–290
  toxicity, 291–292
  uses, 288
    in cardiac arrhythmias, 299–302
    in heart-block, 302
    in heart failure, 292–293
Digitoxin, 289, 290. *See also* Digitalis
Digoxin, 288, 290. *See also* Digitalis
Dihydrocodeine, 166
Dihydroergotamine, 155
Dihydrostreptomycin, 42
Dihydrotachysterol, 406. *See also* Vitamin D
Di-iodohydroxyquin, in amœbiasis, 73
  in vaginitis, 71
Di-isopropyl fluorophosphate, 236
  poisoning, 234–235
DILANTIN: phenytoin
DILAUDID: hydromorphone
Dill, 318
DIMENFORMON: œstradiol monobenzoate
Dimenhydrinate, 219, 335. *See also* Anti-emetics and Antihistaminics
Dimercaprol, 431
Dimethisterone, 358
Dimethyl cysteine, 432
Dimethyl phthalate, 418
Dimethyl tubocurarine, 138
DIMYCIN: streptoduocin
DINDEVAN: phenindione
Dinitro-compounds, poisoning, 433
Dinitrophenol, 433
DIODOQUIN: di-iodohydroxyquin
DIONIN: ethylmorphine
DI-PARALENE: chlorcyclizine
DIPARCOL: diethazine
Diphemanil, 244
Diphenadione, 343. *See also* Anticoagulants
DIPHENATIL: diphemanil
Diphenhydramine, 219, 335. *See also* Anti-emetics and Antihistaminics
  uses, Parkinsonism, 247
Diphenylhydantoin. *See* Phenytoin
Diphtheria, 57
Dipipanone, 166
Disease and drugs, 440–441
DISECRON: progesterone
DISIPAL: orphenadrine
DISPRIN: aspirin, soluble
Disseminated lupus erythematosus, 99
DISTAQUAINE: penicillin
DISTAVAL: thalidomide
Distribution of drugs, 435
Disulfiram, 194–195
Dithiazanine, 85
Dithranol, 418, 425, 426
Diuretics, 304–314
  assessment, 304–305
  choice of, 313–314
  failure of, 314
  use in heart failure, 292–293
Divinyl ether, 129
Dizziness, 221
DOCA. *See* Deoxycortone
DOLANTIN: pethidine
Domiphen, 426
DORIDEN: glutethimide
DORMINAL: amylobarbitone sodium
DORNOKINASE: streptokinase and streptodornase
DORYL: carbachol
Dosage, 434
Double-blind technique, 13
Dover's powder, 157
DRAMAMINE: dimenhydrinate
DRINAMYL, 210
DROMORAN: levorphanol
Drug addiction. *See* Addiction
Drug, combinations, 439
  development, 9–11
  names, 454–456
  therapy, 1–5
Drunkenness, 193–195
DULCOLAX: bisacodyl
Dummy tablets, 5
Duodenal ulcer. *See* Peptic ulcer
Dusting powders, 417

Dyflos, 236. *See also* Choline drugs
Dysentery, amœbic. *See* Amœbiasis
  bacillary, 61
Dysmenorrhœa, 356–357
  amphetamine in, 209
  progesterone in, 358
Dystrophia myotonica, 149

Ear drops, 419
ECOLID: chlorisondamine
Ectopic beats, 299
Eczema, 426
Edrophonium, 236. *See also* Choline drugs
  in myasthenia, 238
EF-CORTELAN: hydrocortisone
EF-CORTELAN INTRAVENOUS: hydrocortisone sodium succinate
EF-CORTELAN SOLUBLE: hydrocortisone hemisuccinate
Effervescent powder, 315
Electrocortin. *See* Aldosterone
ELKOSIN: sulphasomidine
ELORINE: tricyclamol
ELTROXIN: *l*-thyroxine sodium
EMBEQUIN: di-iodohydroxyquin
Embolism, 348
Emesis, therapeutic, 221
Emetics, 219, 221
Emetine, 72–73
Emetine bismuth iodide, 73
Emodin, 323
EMPIRIN: aspirin
Empyema, 58–59
  intrapleural penicillin, 41
Emulsifying ointment, 417
ENAVID: norethynodrel
Endocarditis, 59–60
  prophylaxis, 60
Endometriosis, 358
Enemas, 326
ENTACYL: piperazine
"Enteric" coated preparations, 436
Enteritis, 61
Enterobius, 84
Enuresis, 244, 255
EPANUTIN: phenytoin sodium
Ephedrine, 254–255. *See also* Sympathomimetics
  in migraine, 156
  uses, asthma, 257–258
    dimercaprol toxicity, 431
Ephedrine—*continued*
  uses, myasthenia, 238
Epilepsy, 111–116
  choice of drug, 115
  mephenesin in, 207
Epinephrine. *See* Adrenaline
Epistaxis, 339
Epsom salts, 320
EPTOIN: phenytoin sodium
EQUANIL: meprobamate
Ergocalciferol, 406. *See also* Vitamin D
Ergometrine, 360–363
  in migraine, 155–156
Ergonovine, 360. *See* Ergometrine
Ergot, 360–363
  adrenergic block, 267
Ergotamine, 360–363
  in migraine, 155
Ergotoxine, 363
ERGOTRATE: ergometrine
Erysipelas, 56, 425
ERYTHROCIN: erythromycin
Erythromycin, 47–48
  Gram-staining and, 23
  uses, in amœbiasis, 73
    in diphtheria, 57
    in staphylococcal infections, 54, 55
Erythrytyl tetranitrate, 264. *See also* Nitrates
Eserine. *See* Physostigmine
ESIDREX: hydrochlorothiazide
ESKACILLIN: penicillin
ESTIGYN: ethinylœstradiol
Ethanol. *See* Alcohol
Ether, 128–129. *See also* Anæsthetics
  addiction, 186
  diabetes and, 149
ETHIDOL: ethinylœstradiol
ETHNINE: pholcodine
ETHODRYL: diethylcarbamazine
Ethopropazine, 246–247
Ethinylœstradiol, 355 *See also* Œstrogens
Ethisterone, 358
Ethyl alcohol. *See* Alcohol
Ethyl biscoumacetate, 343, 344. *See also* Anticoagulants
Ethyl chloride, 120
Ethyl ether, 128–129. *See also* Anæsthetics
Ethylenediamine, 225, 226
Ethylenimines, 412

Ethylmorphine, 167
Ethylnoradrenaline, 254
ETICYCLIN: ethinylœstradiol
Eucatropine, 244
EUMYDRIN: atropine methonitrate
EURAX: crotamiton
Eusol, 419
Evacuant. *See* Purgative
EVIPAN: hexobarbitone
Exfoliative dermatitis, 99, 427
Exophthalmos, 365
Expectorants, 215–217
Extrinsic factor, 391
Eye disease, adrenocortical steroids in, 99
Eye infections, 68–69
Eye washes, 419

Factor V, 337
Factor VII, 337
Fate of drugs, 435
Favism, 444
^{59}**Fe,** 386
Febrile convulsions, 116
FEBRILIX: paracetamol
FEMANDREN, 356
FEMERGIN: ergotamine
FENTAZIN: perphenazine
FERCUMAN: ferrous sulphate
FERGON: ferrous gluconate
FERLUCON: ferrous gluconate
FEROSAN: ferrous sulphate
Ferric ammonium citrate, 388. *See also* Iron
Ferric hydroxide, 388. *See also* Iron
FERRIVENIN: saccharated iron oxide
FERRONICUM: ferrous gluconate
Ferrous carbonate, 388. *See also* Iron
Ferrous gluconate, 388. *See also* Iron
Ferrous sulphate, 388. *See also* Iron
FERSOLATE: ferrous sulphate
Fibrillation, 300–301
Fibrin, 338, 339
Fibrinogen, 338
Fibrocystic disease, 354
Figs, 320
Filariasis, 86
Filix mas, 84
Fish-liver oil, 399, 407
FLAXEDIL: gallamine
FLEXIN: zoxazolamine
FLORINEF: fludrocortisone
Fludrocortisone, 93. *See also* Adrenocortical hormones
  in corticotrophin test, 89
  on the skin, 423
FLUOTHANE: halothane
Fluoxymesterone, 353–354
Fœtus, drugs and, 147–148
Folic acid, 394–395
  antagonists, 413
  sulphonamides and, 31
Folinic acid, 324
Follicular lymphoma, 411
FRENQUEL: azacyclonol
Friars' balsam, 214
Fructose, 194
FULCIN: griseofulvin
Fungi, 233–234
FURADANTIN: nitrofurantoin
Furaltadone, 63

Gallamine, 119, 138. *See also* Neuromuscular blocking agents
Ganglion-blocking drugs, 270–275, 279–282
  uses, hiccough, 205
    vasodilator, 269
GANTRISIN: sulphafurazole
GARDENAL: phenobarbitone
Gargles, 419
Gastric secretion, histamine and, 330–331
Gastric ulcer. *See* Peptic ulcer
Gastrin, 330
Gee's linctus, 162
Gelatin sponge, 339
Gelsemium, 154
GEMONIL: metharbital
GENASPIRIN: aspirin
GENOPHYLLIN: aminophylline
Genoscopolamine, 242
Gentian, 318
Gentian and acid mixture, 6
Gentian violet, 426
GESTONE: progesterone
GESTONE-ORAL: ethisterone
Giant-cell arteritis, 99
GLANDUATRIN: gonadotrophin, chorionic
GLANDUBOLIN: œstrone
GLANDUBOLIN-MONOBENZ: œstradiol monobenzoate

GLANDUCORPIN: progesterone
Glauber's salt, 320
Glaucoma, acetazolamide in, 310
Glomerular filtration rate, 313
GLOSSO-STERANDRYL: methyltestosterone
Glucocorticoid effects, 92, 93, 94
Glucose, 313
Glutethimide, 107
Glyceryl trinitrate, 263. *See also* Nitrates
GLYCODINE: pholcodine
Goitre, 366–374
Gold, **177–178,** 431
Gonadotrophins, 351
GONADOTRAPHON L.H.: chorionic gonadotrophin
GONADYL CHORIONIC: gonadotrophin, chorionic
GONAN: gonadotrophin, chorionic
Gonorrhœa, 69
Gout, 178–181
Gram-staining, 22–23
Gramicidin, 50
Grand mal, 115
Granulocytopenia, 446
Granuloma inguinale, 71
Grey powder, 324
Griseofulvin, **51,** 425
GRISOVIN: griseofulvin
Growth hormone, **351**
  versus insulin, 379
Guaiacols, 215
Guanethidine, 270

Habituation, 183–185
Hæmochromatosis, 390
Hæmolysis, 444, 446
Hæmophilia, 338
Hæmorrhagic disease of the newborn, 340
Hæmostatics, 338–339
Hallucinogen, 101
Halothane, 131
  addiction to, 186
Hamamelis, 326
HARMONYL: deserpidine
Hashish, 212
Hay fever, 333–334
Headache, 155
Heart, arrhythmias, 298–303
  autonomic nervous effects on, 298–299
Heart failure, 292–293
Heart-block, 302
Heavy-metal poisoning, 431–432
HELMEZINE: piperazine
Hemp, Indian, 212
Heparin, 341–342, 344. *See also* Anticoagulants
Hepatic failure, drugs in, 440
  neomycin in, 49
  sedation in, 160
Hepato-lenticular degeneration, 432
HEPTALGIN: phenadoxone
Heroin, 164–165. *See also* Opiates
Herpes simplex, 427
Herpes zoster, 155, 427
Herxheimer reaction, 70, 444
HETP, 236
  poisoning, 234–235
HETRAZAN: diethlycarbamazine
HEWŒSTROL: ethinylœstradiol
Hexadimethrine, 342
Hexaethyl tetraphosphate, 236
  poisoning, 234–235
Hexamethonium, 270, 272. *See also* Ganglion-block
Hexamine, 63
Hexamine mandelate, 63
Hexobarbitone, 104. *See also* Barbiturates
Hexobarbitone sodium, 133
Hexœstrol, 355
HEXOPAL, 265
Hexylresorcinol, 84, 85
Hiccough, 205
Histaminase, 332
Histamine, 330–332
  test of gastric function, 330–331
  test for phæochromocytoma, 282
Histamine liberators, 330
HISTANTIN: chlorcyclizine
Hodgkin's disease, 410, 414
Homatropine, 243
Hookworm, 85
HORMOFEMIN: dienœstrol
Hormones. *See* individual hormones
Hunner's ulcer, 100
HYALASE: hyaluronidase
Hyaluronidase, **437**
  with local analgesics, **141**
HYDERGINE, 267, 363
HYDRENOX: hydroflumethiazide
HYDRIL: hydrochlorothiazide
Hydantoins, 113

Hydralazine, 278
HYDRO-ADRESON: hydrocortisone
Hydrochloroquine, in arthritis, 177
Hydrochlorothiazide, 308
Hydrocodone, 166
Hydrocortisone, 92, 93. *See also* Adrenocortical hormones
  use, anaphylaxis, 445
    antipruritic, 421
    congenital syphilis, 69
    eye infections, 69
    hypotension, 260
    skin diseases, 422–423, 425–428
HYDROCORTISTAB: hydrocortisone
HYDROCORTISYL: hydrocortisone
HYDROCORTONE: hydrocortisone
HYDRODELTALONE: prednisolone acetate
Hydroflumethiazide, 308
Hydrogen peroxide, 419
  in cyanide poisoning, 432
Hydromorphone, 166
HYDROSALURIC: hydrochlorothiazide
Hydroxyamphetamine, 256
Hydroxydione, 133
Hydroxystilbamidine, 72
Hydroxyzine, 207
Hyoscine, 242–243. *See also* Anticholines
  uses, anti-emetic, 217–219
    in hiccough, 205
    mania, 210
    Parkinsonism, 247
    in premedication, 125
Hyoscine butylbromide, 243
Hyoscine hydrobromide, 242
Hyoscine methobromide, 243
Hyoscyamine, 242. *See also* Anticholines
Hyoscyamus, 242–243
Hyperactive states. *See* Mania
Hypercalcæmic syndrome, 316
Hyperhidrosis, 268, 428
  propantheline in, 244
Hypersensitivity reactions, 444–448
Hypertension, 279–283
Hypertensive encephalopathy, 271, 272, 281
Hyperthyroidism, 367–374
Hypnotic, 101–110
  definition, 101
Hypnotic—*continued*
  poisoning, 109
Hypoglycæmia, 378
Hypoglycæmic drugs, oral, 383–384
Hypopituitarism, 96–97, 352
  corticotrophin test in, 89–90
Hypotension, in anæsthesia, 273
Hypotensive drugs, 262–283
Hypotensive states, 258–260

^{131}I, 371. *See also* Antithyroids
  in angina, 266
Ichthammol, 418
ICIPEN V: phenoxymethylpenicillin
Idiosyncrasy, 444
ILOTYCIN: erythromycin
IMFERON, 388–389
Imipramine, 210
Impetigo, 425
Impotence, 353
Incompatibility, 453
INDEMA: phenindione
Indian hemp, 212
Individual variation, 439
Infertility, progesterone in, 358
INH. *See* Isoniazid
Inositol, 399
Insect bites, 418–419
Insect repellants, 418
Insecticide, poisoning by, 234–235, 433
Insulin, 375–383
  actions, 375–376
  preparations, 376–378
  surgery and, 459–460
  toxicity, 378
Intertrigo, 428
Intolerance, 439, 443–444
INTRAVAL SODIUM: thiopentone sodium
Intrinsic factor, 391, 393–394
Inulin, 313
INVERSINE: mecamylamine
Iodide, 367–369
  uses, in cough, 216
    expectorant, 215
    in syphilis, 70
Iodine, radioactive, 371. *See also* Antithyroid
  solution, 368
  toxic effects, 369
Ion-exchange resins, 311–312

Ipecacuanha, 6, 72, 215
Ipecacuanha and opium tablets, 157
Iproniazid, 65, 209, 210, 265
Iron, 385–390
Iron chelates, 390
Iron-dextran complex, 388–389
IRONATE: ferrous gluconate
Irritant vapours, 224
ISMELIN: guanethidine
Isoniazid, 64–68
  in actinomycosis, 72
Isoprenaline, 249–252, 254
  uses, asthma, 257–258
Isopropylnoradrenaline. *See* Isoprenaline
Isoproterenol. *See* Isoprenaline
ISUPREN: isoprenaline
Itching, 421
IVIRON, saccharated iron oxide

Jalap, 323
Jarisch-Herxheimer reaction, 70
Jaundice, androgens in, 359

Kala-azar, 82
Kanamycin, 51
Kaolin, 315, 327
  poultice, 420
KAPILON: acetomenaphthone
KATONIUM, 312
KEMADRIN: procyclidine
KEMITHAL: thialbarbitone sodium
Keratolytics, 418, 426
Khellin, 265
KOLANTYL: dicyclomine
KONAKION: Vitamin K_1
KWELLS: hyoscine hydrobromide

Lachesine, 244
Lactation, suppression, 357
Lanatoside C, 289, 290. *See also* Digitalis
LANOXIN: digoxin
LARGACTIL: chlorpromazine
Lassar's paste, 418, 426
Laudanum, 162
Laudexium, 138. *See also* Neuromuscular blocking agents
LAUDOLISSIN: laudexium
Laxative. *See* Purgative
Lead, poisoning, 432
Lead lotion, 416
LEDERCORT: triamcinolone
LEDERKYN: sulphamethoxypyridazine
LEDERMYCIN: demethylchlortetracycline
Leishmaniasis, 82
Leprosy, 82–83
Leptazol, 222
  in barbiturate poisoning, 110
Leptospirosis, 83
LERGINE: tricyclamol
LETHIDRONE: nalorphine
LEUCARSONE: carbasone
LEUCOVORIN: folinic acid
Leukæmia, 409–415
LEUKERAN: chlorambucil
Levallorphan, 167
  with pethidine, 147
Levarterenol. *See* Noradrenaline
Levorphanol, 166
LEVOPHED: noradrenaline
Lichen planus, 428
Lichen simplex, 428
Lignocaine, 143, 145–146. *See also* Local analgesics
LIGNOSTAB: lignocaine
Liniments, 420
Liothyronine, 365–367
Liquid paraffin, 319, 321
Liquorice, 214
Lithium, 305
Liver extracts, 394
Liver failure, androgens in, 354
Lobeline, 224
Local anæsthetics, 140–146
Local analgesics, 140–146
  absorption, 141–142
  action, 140–141
  choice of, 146
  toxicity, 142–143
  uses, 142
Long-acting preparations, 435–436
LORFAN: levallorphan
Lotions, 416–417
Low-salt diets, 305
LSD, 212
Lucanthone, 83
LUCIDIL: benactyzine
Lugol's solution, 368, 370
LUMINAL: phenobarbitone
Lupus erythematosus, 427

Lupus vulgaris, 67
LUTEOSTAB: progesterone
LUTOCYCLIN: progesterone
LUTOCYCLIN LINGUETS: ethisterone
LUTOFORM: progesterone
Lymphogranuloma venereum, 71
LYNORAL: ethinylœstradiol
LYOVAC SALURIC: chlorothiazide (for i.v. use)
Lysergic acid diethylamide, 212
LYSIVANE: ethopropazine
LYTENSIUM: pentamethonium

M and B 693: sulphapyridine
Magenta paint, 425, 426
MAGNAMYCIN: carbomycin
Magnesium, poisoning, 321
Magnesium carbonate, 316
Magnesium hydroxide, 319, 321
Magnesium oxide, 316
Magnesium sulphate, 298, 319, 320, 325
  enemas, 326
  paste, 425
Magnesium trisilicate, 315–316, 317
Malabsorption syndromes, folic acid in, 395
Malaria, 74–78
Male fern, 84
MALIDONE: aloxidone
MANDELAMINE: hexamine mandelate
Mandelic acid, 63
Manganese, 390
Mania, 210
Mannitol, 313
Mannityl hexanitrate, 264. *See also* Nitrates
MAPHARSIDE: oxophenarsine
MARCOUMAR: phenylpropylhydroxycoumarin
Marihuana, 212
MARSILID: iproniazid
MARZINE: cyclizine
Masking of infections, 27–28
MATROMYCIN: oleandomycin
Measures, 450
Mecamylamine, 272–273. *See also* Ganglion block
Mechlorethamine, 410–411, 414
Mecholyl. *See* Methacholine
MECHOTHANE: bethanechol
Meclozine, 219. *See also* Antiemetics
MEDINAL: barbitone sodium
MEDRONE: methylprednisolone
MEGIMIDE: bemegride
MEMINE: pholcodine
Menaphthone, 340
MENFORMON: œstrone
Meningitis, 60
Menopausal symptoms, 356
Menstrual disorders, 356, 358
Mental disorder, 200–211
Menthol, 224, 421
Menthyl salicylate, 423
Mepacrine, 77
  dosage, 457–458
  history, 75
  uses, worms, 84
    lupus erythematosus, 427
MEPAVLON: meprobamate
Meperidine. *See* Pethidine
Mephenesin, 206, *See also* Tranquillisers
  uses, hiccough, 205
    myoclonic epilepsy, 112
    strychnine poisoning, 222
    tetanus, 119
Mephentermine, 256
MEPHINE: mephentermine
MEPHYTON: Vitamin K_1
MEPILIN, 356
Meprobamate, 206–207. *See also* Tranquillisers
  uses, painful muscle spasm, 154
    psychoneurosis, 211
Mepyramine, 335. *See also* Antihistaminics
  in histamine test, 330
MERATRAN: pipradrol
Merbaphen, 306
MERBENTYL: dicyclomine
Mercaptomerin, 307
Mercaptopurine, 413, 414
MERCARDAN: meralluride
MERCLORAN: chlormerodrin
Mercurial diuretics, 306–308. *See also* Diuretics
Mercuric nitrate ointment, 420
Mercurochrome, 71
Mercury, 323–324
  poisoning, 431
Mersalyl, 307. *See also* Diuretics

Mescaline, 211–212
MESONTOIN: methoin
MESTINON: pyridostigmine
METAMINE: triethanolamine trinitrate
Metaraminol, 256
METARSENOBILLON: sulpharsphenamine
Methacholine, 232. *See also* Choline drugs
Methadone, 164. *See also* Opiates
Methæmoglobinæmia, 405
Methallenœstril, 355
Methamphetamine, 209. *See also* Sympathomimetics
Methandriol, 359
Methanol, 196–197
Methantheline, 244
Metharbital, 113
METHEDRINE: methylamphetamine
Methenamine, 63
METHERGIN: methylergometrine
Methoin, 113
Methonium drugs, 270
Methotrexate, 413, 414
Methoxamine, 256, 259
Methoxyphenamine, 255
Methyl alcohol, 196–197
Methyl phenidate, 209
Methyl salicylate, 173, 420
Methylamphetamine, 255. *See also* Sympathomimetics
Methylandrostanolone, 359
Methylcellulose, 319, 320
Methyldihydromorphinone, 166
Methylene blue, 405
Methylergometrine, 362
Methylmorphine. *See* Codeine
Methylpentynol, 107
Methylphenobarbitone, 103, 104. *See also* Barbiturates
  as anticonvulsant, 113
Methylprednisolone, 92, 93. *See also* Adrenocortical hormones
Methyprylone, 107
Methyltestosterone, 353–354
Methylthiouracil, 370
Metropathia, 356
MICTINE: aminometradine
Migraine, 155–156
MIGRIL: ergotamine
Milk, drugs in, 435
MILLICORTEN: dexamethasone
MILONTIN: phensuximide
MILTOWN: meprobamate
Mineralocorticoid effects, 92, 93, 94
Miotics, 235, 236
MIRACIL D: lucanthone
MIXOGEN, 356
MIXTAMYCIN: streptoduocin
Mode of action of drugs, 438
Molybdenum, 390
MONARGAN: acetarsol
Monilia, 50, 426
  vaginitis, 71
Mono-amine oxidase inhibitors, 209–210
MONODRAL: penthienate
Morphine, 158–162. *See also* Opiates
  amiphenazole and, 224
  antagonists, 167
  histamine liberator, 330
  history, 157
  uses, heart failure, 292
    mania, 210
    paralytic ileus, 326
    premedication, 125
MORYL: carbachol
Motion sickness, drugs in, 217–219
Mouthwashes, 419
Mumps, orchitis, 100
Muscarine, 233
Muscarinic effects, 230
Muscle relaxants. *See* Neuromuscular blocking agents
Muscle spasm, 154
  mephenesin in, 206
  meprobamate in, 207
  neostigmine in, 236
Muscular relaxation, 134
"Mushroom" poisoning, 233–234
Mustard plasters, 420
Mustine, 410–411, 414
MYANESIN: mephenesin
Myasthenia, 236–238
  neuromuscular block in diagnosis, 139–140
  quinine in, 78–79
MYBASAN: isoniazid
MYCARDOL: pentaerythritol tetranitrate
MYCIFRADIN: neomycin
Mycosis fungoides, 410
MYCOSTATIN: nystatin
Mydriatics, 244
  atropine, 240

Mydiatrics—*continued*
  ephedrine, 255
  homatropine, 243
  hyoscine, 242
  phenylephrine, 255
Myeloma, 414
MYLERAN: busulphan
Myocardial infarction, 346–347
  sympathomimetics in, 259
MYOCRISIN: sodium aurothiomalate
Myotonia, 78
MYSOLINE: primidone
Myxœdema, 365–366
  coma, 366
  ^{131}I test for, 371
  therapeutic, 374

NACLEX: hydroflumethiazide
Nalorphine, 162, 167
Names, 454–456
Naphazoline, 256
Narcolepsy, 208, 211
Narcotic, definition, 101
Narcotic analgesics. *See* Opiates
Narcotine, 165
NARDIL: phenelzine
Nasal decongestants, 255–257
NATIVELLE'S CRYSTALLISED DIGITALINE: digitoxin
NEMBUTAL: pentobarbitone sodium
Neoarsphenamine, 80. *See also* Arsenicals
NEOBACRIN: bacitracin with neomycin
NEO-CORTEF: hydrocortisone acetate
NEODRENAL: isoprenaline
NEO-EPININE: isoprenaline
NEO-FERRUM (INTRAVENOUS): saccharated iron oxide
NEO-HOMBREOL: testosterone propionate
NEO-MERCAZOLE: carbimazole
NEOMIN: neomycin
Neomycin, 49
  uses, colonic surgery, 61
    intra-articular, 177
    skin infections, 422
NEOPHRYN: phenylephrine
Neosalvarsan. *See* Neoarsphenamine
Neostigmine, 235–238. *See also* Choline drugs
Neostigmine—*continued*
  uses, tubocurarine antagonist, 137–138
    vasodilator, 269
NEOSYNEPHRINE: phenylephrine
NEPENTHE: morphine
Nephritis, prophylaxis, 56
Nephrotic syndrome, 99, 312
  chemoprophylaxis in, 56
Nerve block, 142
NEUMANDIN: isoniazid
Neuralgia, 154
Neurodermatitis, 421, 428
Neuromuscular block, agents, 133–140
    in neonates, 150
    in obstetrics, 147
  uses, 139–140
Neuromuscular transmission, 135
Neuroses, 211
New drugs, 9–11
NICETAL: isoniazid
Nicotinamide, 402. *See also* Vitamin B
Nicotine, 187
Nicotinic acid, 402
Nicotinic acid amide, 402
Nicotinic effects, 230
Nikethamide, 223
  in barbiturate poisoning, 110
NILEVAR: norethandrolone
NILODIN: lucanthone
NISENTIL: alphaprodine
Nitrates, 262–265
Nitrites, 262–265
Nitrofurantoin, 62
Nitrogen mustards, 410–411
Nitroglycerin, 263
Nitrous oxide, 129–130. *See also* Anæsthetics
  addition to, 186
  in labour, 147
NIVAQUINE: chloroquine
NIVEMYCIN: neomycin
NOLUDAR: methyprylone
Noradrenaline, 249–254, 259
Norandrostenolone, 359
Norepinephrine. *See* Noradrenaline
Norethandrolone, 359
Norethisterone, 358
Norethynodrel, 358
NORISODRINE: isoprenaline
Noscapine, 165, 215

NOTENSIL: acepromazine
NOVARSENOBILLON: neoarsphenamine
NOVESTRINE: methallenœstril
Novobiocin, 50, 54, 55
NOVOCAIN: procaine
NOVUTOX: procaine
Nucleotoxic drugs, 409–415
NUPERCAINE: cinchocaine
Nux vomica, 318
NYDRANE: benzchlorpropamide
NYDRAZID: isoniazid
Nylidrin, 265
Nystatin, 50, 422, 426

Obesity, amphetamine in, 208
  phenmetrazine in, 209
  thyroid in, 366
OBLIVON: methylpentynol
Obstetric analgesia, 146
Octamethyl pyrophosphoramide, 236
  poisoning, 234–235
Octyl nitrite, 263–264. *See also* Nitrites
Oculogyric crises, 247
Œsophageal achalasia, 263–264
Œsophagitis, 316
Œstradiol, 355. *See also* Œstrogens
ŒSTROFORM AMPOULES: œstradiol monobenzoate
Œstrogens, 354–358
  and the skin, 423
  uses in, aggression, 211
    vaginitis, 71
Œstrone, 355. *See also* Œstrogens
Oil of wintergreen, 173
Oily cream, 417
Ointments, 417
Oleandomycin, 51, 54
OMNOPON: papaveretum
OMPA, 236
  poisoning, 234–235
Opiates, 162–167
  antagonists, 167
  and the fœtus, 147
  uses, analgesic, 157
    cough, 215, 216
    diarrhœa, 327
Opium, 157
  addiction, 160, 185
  alkaloids, 157
Opium—*continued*
  tincture, 162
ORADEXON: dexamethasone
ORALUTON: ethisterone
ORARSAN: acetarsol
ORAVIRON: methyltestosterone
Organic arsenicals, 80
Organic mercurials. *See* Mercurial diuretics
ORISULF: sulphaphenazole
Orphenadrine, 246–247
Orthocaine, 146
ORTHOXINE: methoxyphenamine
ORTIN: triethanolamine trinitrate
Osmotic diuretics, 312–313
OSTELIN: calciferol
Osteoarthritis, 178
Osteomalacia, 405–407
Osteomyelitis, 71–72
Osteoporosis, 359–360
Otitis, 56
OTOPHEN: chloramphenicol
Ouabain, 289, 290. *See also* Digitalis
Overdosage, 443
OVOCYCLIN: œstradiol monobenzoate
Oxalate, 337
Oxazolidinediones, 113
Oxeladin, 215
Oxidised cellulose, 339
Oximes, 235
Oxophenarsine, 80
Oxtriphylline. *See* Choline theophyllinate
OXYCEL: oxidised cellulose
Oxyphenonium, 244
Oxygen therapy, expectorants in, 217
Oxytetracycline, 46–47. *See also* Tetracyclines
Oxytocin, 353, 362
Ox bile, 319

^{32}**P**, 413, 414
P2S, 235
PABESTROL: stilbœstrol
PACATAL: pecazine
PAGITANE: cycrimine
Pain, 151–181
PALFIUM: dextromoramide
PALUDRINE: proguanil
PAM, 235
Pamaquine, 77

PAMINE BROMIDE: hyoscine methobromide
PANADOL: paracetamol
Pancreatin, 318
Pancreatitis, 159
PANTESTIN: testosterone propionate
PANTESTIN ORAL: methyltestosterone
Pantothenic acid, 399
Papain, 318
Papaverine, 165, 269
Papaveretum, 162
  in premedication, 125
Para-aminobenzoic acid, 31, 399, 423
Para-aminosalicylic, 64–68
Paracetamol, 173. *See also* Analgesics
PARADIONE: paramethadione
Paraldehyde, 102–103
  uses, 108
    basal narcosis, 131
    hepatic failure, 160
    mania, 210
    status epilepticus, 115
    tetanus, 119
Paraffin. *See* Liquid paraffin
Paralytic ileus, 326
Paramethadione, 113, 115
Parasympathomimetics. *See* Choline drugs
Parathion, 236
  poisoning, 235
Parathyroid hormone, 405–406
Paratyphoid, 45
PAREDRINEX: hydroxyamphetamine
Parkinsonism, 245–248
  amphetamine in, 209
  belladonna in, 242–243
  chlorpromazine induced, 205
  mephenesin in, 207
  meprobamate in, 207
Paronychia, 426
Paroxysmal nocturnal dyspnœa, 226
Paroxysmal tachycardia, 299–300
PARPANIT: caramiphen
PAS, 64–68
Pastes, 418
Patch tests, 447
Pecazine, 206
PECTAMOL: oxeladin
Pectin, 327, 342
Pediculosis, 426
Pellagra, 402
Pemphigus, 99, 427
Pempidine, 273. *See also* Ganglion block
  in hypertension, 281
PENAVLON V: phenoxymethylpenicillin
Penicillamine, 432
Penicillin, 36–41
  desensitisation, 38–39
  dosage, 39–41
  Gram-staining and, 23
  history, 19–20
  inhalations, 41
  intrapleural, 41
  intrathecal, 41
  lozenges, 37, 41
  resistance, 39
  toxic effects, 37–39
  uses, 39
    actinomycosis, 72
    bronchitis, 57
    chancroid, 71
    chickenpox, 72
    diphtheria, 57
    empyema, 41
    endocarditis, 59–60
    eye infections, 68
    gonorrhœa, 69
    meningitis, 60
    pneumonia, 58
    Proteus infections, 62
    rheumatic fever, 175
    sore throat, 55
    staphylococcal infections, 54, 55
    streptococcal infections, 55–56
    syphilis, 69–70
    tetanus, 117, 119
    typhoid carriers, 45
    Vincent's angina, 57
Penicillin G. *See* Benzylpenicillin
PENICILLIN V: phenoxymethylpenicillin
PENIDURAL: benzathine penicillin
Pentaerythrytol tetranitrate, 264. *See also* Nitrates
Pentamethonium, 138, 270
Pentamidine, 80–82
Pentaquine, 76–77
  dosage, 457–458
Penthienate, 244
Pentobarbitone sodium, 104. *See also* Barbiturates
Pentolinium, 274

PENTOTHAL: thiopentone sodium
PENVIKAL: phenoxymethylpenicillin
Peppermint, 318
Peptic ulcer, 317–319
  anticholines in, 243
  ganglion-blockers in, 272
PERANDREN: testosterone
PERANDREN INJECTION: testosterone propionate
PERANDREN LINGUETS: methyltestosterone
Perchlorate, 371. *See also* Antithyroids
PERCORTEN: deoxycortone acetate
PERDILATAL: nylidrin
Peripheral neuritis, cyanocobalamin in, 393
Peripheral vascular disease, 268–269
  histamine in, 331
  tolazoline in, 266–267
Peritonitis, 60
PERITRATE: pentaerythritol tetranitrate
Pernicious anæmia, 392, 395
PERNIVIT: acetomenaphthone
PEROLYSEN: pempidine
Perphenazine, 206
PERSOMNIA, 107
Personality, drugs and, 441–442
Pethidine, 163. *See also* Opiates
  uses in hiccough, 205
    obstetric, 147
  in premedication, 125
PETHILORFAN, 147
Petit mal, 115
Peyote, 211–212
Phæochromocytoma, 282–283
PHANODORM: cyclobarbitone
Phemitone. *See* Methylphenobarbitone
Phenacemide, 112
Phenacetin, 173
Phenadoxone, 166
Phenazone, 173
Phenelzine, 210
PHENERGAN: promethazine
Phenformin, 384
Phenindamine, 247, 335. *See also* Antihistaminics
Phenindione, 343, 344. *See also* Anticoagulants
Pheniprazine, 210
Phenmetrazine, 209
Phenobarbitone, 103–105. *See also* Barbiturates
  history, 111
  uses, as anticonvulsant, 113, 115, 116
    asthma, 257
    prophylaxis, 111
Phenol, as antipruritic, 421
Phenolphthalein, 319, 322, 324
Phenothiazines, 204–206
  use as anti-emetics, 220
Phenoxybenzamine, 267
  in phæochromocytoma, 283
Phenoxymethylpenicillin, 40. *See also* Penicillin
Phensuximide, 113, 115
Phentolamine, 267
  test for phæochromocytoma, 282
  in noradrenaline overdose, 253
PHENURONE: phenacemide
Phenylbutazone, 174
  peptic ulcer and, 317
  uses, gout, 180–181
Phenylephrine, 255, 259
Phenylethyldiguanide, 384
Phenylhydrazine, 413
Phenylmercuric nitrate, 71
Phenylpropanolamine, 256
Phenylpropylhydroxycoumarin, 343. *See also* Anticoagulants
phenylpropylmethylamine, 256
Phenytoin, 113–116
Pholcodeine, 166, 215–216
Phosphates, as tonics, 7
PHRENAZOL: leptazol
Phthalylsulphathiazole, 35. *See also* Sulphonamides
PHYSEPTONE: methadone
Physostigmine, 235. *See also* Choline drugs
Phytonadione. *See* Vitamin K_1
Picrotoxin, 222
  in barbiturate poisoning, 110
Pilocarpine, 233. *See also* Choline drugs
Pink disease, ganglion-block in, 275
PIPADONE: dipipanone
PIPANOL: benzhexol
Piperazine, 84
Pipradrol, 200
PIRITON: chlorpheniramine
PITOCIN: oxytocin
PITRESSIN: vasopressin

Pituitary hormones, 351–353
  corticotrophin, 88–91
  thyroid stimulating, 365
Pityriasis rosea, 428
Placebos, 5–7
Plague, 83
PLAQUENIL: hydroxychloroquine
Plasma, triple strength, 313
Platelet deficiency, 338
Pneumonia, 57–58
  prophylaxis, 58
Podophyllin, 418
Podophyllum, 323
Poisoning, 429–433. *See also* individual drugs
Polyarteritis nodosa, 99, 446
POLYBRENE: hexadimethrine
Polycythæmia, 413
POLYFAX: bacitracin with polymyxin B
Polymyxin, 49
  uses, skin infections, 422
    urinary infections, 62
Polyneuritis, 100
Porphyria, 105, 441
  anæsthesia in, 149
Potassium, adrenocortical steroids and, 94
  digitalis and, 285
  poisoning, 312
  poisoning, lactate in, 302
  uses, diabetic ketosis, 382
    digitalis poisoning, 291
Potassium bicarbonate, 315
Potassium bromide, 105–107
Potassium chloride, with chlorothiazide, 308
Potassium citrate, 62, 315
Potassium iodide, 367–368
Potassium permanganate, 416
  in cyanide poisoning, 432
Potassium sulphide, 432
Potentiation, 438
Powders, 417
PRÆNITRONA: triethanolamine trinitrate
PRE-CORTISYL: prednisolone
PRECORTISYL INTRAVENOUS: prednisolone hemisuccinate
Prednisolone, 92, 93. *See also* Adrenocortical hormones
Prednisone, 92, 93. *See also* Adrenocortical hormones
Pregnancy, anti-emetics in, 220
  folic acid in, 395
  iron in, 387
PREGNYL: chorionic gonadotrophin
PRELUDIN: phenmetrazine
PREMARIN, 355
Prematurity, 407
  iron in, 387
Premedication, 124–126
Premenstrual syndrome, progesterone in, 358
PRENOLONE: prednisolone
Prescribing, 451–453
Primaquine, 76–77, 444
  dosage, 457–458
Primidone, 113, 115
PRIMODIAN-DEPOT, 357
PRIMOGYN-DEPOT: œstradiol valerate
PRIMOLUT-DEPOT, 358
PRISCOL: tolazoline
PRIVINE: naphazoline
PRO-BANTHINE: propantheline
Probenecid, 179–180
  in endocarditis, 59
Procainamide, 297–298
  in cardiac arrhythmias, 299–301
Procaine, 143, 145. *See also* Local analgesics
  at neuromuscular junction, 135
  infusion for pain, 156
Procaine benzylpenicillin, 40. *See also* Penicillin
Prochlorperazine, 206
Procyclidine, 246–247
Proflavine, 420
Progesterone, 358
PROGESTIN: progesterone
Progestogens, 358
PROGESTORAL: ethisterone
Proguanil, 76–77
  dosage, 457–458
PROGYNON B OLEOSUM: œstradiol monobenzoate
PROKAYVIT: menaphthone
PROKAYVIT ORAL: acetomenaphthone
Prolongation of drug effect, 435–436
PROLUTON: progesterone
Promazine, 206
Promethazine, 335. *See also* Antihistaminics
  uses, anti-emetic, 219

Promethazine—*continued*
  uses, hypnotic, 107
    premedication, 125
Promethazine chlorotheophyllinate, 219
PROMINAL: methylphenobarbitone
PRONESTYL: procainamide
Prontosil, 30
PROPADRINE: phenylpropanolamine
Propantheline, 243
Prophylaxis, with antimicrobials, 28–29
Propylhexedrine, 255
Propylthiouracil, 370. *See also* Antithyroids
Prostate, carcinoma, 357
PROSTIGMIN: neostigmine
Protamine, 342
PROTANDREN: methandriol
Protein anabolic agents, 359
Prothrombin, 337
Protoveratrines, 278–279
PROVELL: protoveratrines A and B
Prunes, 320
Pruritus, 421
Pseudomonas, 24
Psittacosis, 58, 83
Psoriasis, 418, 426
Psychomotor epilepsy, 115
Psychomotor stimulants. *See* Antidepressants
Psychoneuroses, 211
Psychoses, 210–211
Psychotomimetics, 101, 211–212
Psychotropic drugs, definition, 101
Psyllium, 319, 320
Pteroylglutamic acid, 394–395
PULARIN: heparin
Pulmonary œdema, 275
  ganglion-block in, 272
Purgatives, 319–326
  addiction, 324
Purine antagonists, 413
PURI-NETHOL: mercaptopurine
PUROVERINE: protoveratrines A and B
PYCAZIDE: isoniazid
Pyloric stenosis, anticholines in, 245
  atropine methonitrate in, 242
PYRAMIDON: amidopyrine
Pyrazinamide, 66
Pyrazolone derivatives, 173–174
PYRIBENZAMINE: tripelennamine
Pyridostigmine, 236. *See also* Choline drugs
  use, myasthenia, 238
Pyridoxine, 403. *See also* Vitalin B
  use, anti-emetic, 220
    alcohol poisoning, 194
Pyrimethamine, 76–77
  dosage, 457–458
Pyruvate metabolism test, 401

Q fever, 58
QUIESCIN: reserpine
QUINACRINE: mepacrine
Quinalbarbitone sodium, 104, 105. *See also* Barbiturates
Quinidine, 293–297
  actions, 293–294
  administration, 295–296
  contra-indications, 294–295
  toxicity, 296–297
  uses, in cardiac arrhythmias, 299–301
  versus procainamide, 298
Quinine, 78–80, 318
  dosage, 457–458
  history, 74
  uses, malaria, 76, 77
    sun-burn, 423
QUINOLOR: chlorhydroxyquinoline

Radiation sickness, 220
Radio-iodine, 371. *See also* Antithyroid
Radio-iron, 386
Radio-phosphorus, 413, 414
Rashes, 446
RASTINON: tolbutamide
RAUDIXIN: rauwolfia
Rauwolfia, 275–278
Raynaud's phenomenon, 268
Regional analgesia, 142
REGITINE: phentolamine
Relapsing fever, 80, 83
Renal failure, 440
  androgens in, 359
Renal tract infections, 61–63
Rescinnamine, 277
RESERPAMED: reserpine
Reserpine, 275–278
  peptic ulcer and, 317
  uses, in hypertension, 281
    mental disorder, 210

RESERPEX: reserpine
Resins, 311–312
RESOCHIN: chloroquine
RESONIUM, 312
Resorcinol, 418
Respiratory depression. *See* Analeptics
Respiratory infections, 57–59
Rheumatoid arthritis, 176–178
Rheumatic fever, 175
  prophylaxis, 56
Rhinitis. *See* Allergic rhinitis
Rhubarb, 323
Riboflavine, 402. *See also* Vitamin B
Ricinoleic acid, 322
Rickets, 405–407
Rickettsial infections, 83
RIMIFON: isoniazid
Ringworm, 425
  griseofulvin in, 51
RISERPA: reserpine
Ristocetin, 51, 54
RITALIN: methyl phenidate
Rochelle salt, 320
ROGITINE: phentolamine
ROLICTON: amisometradine
ROMICIL: oleandomycin
ROMILAR: dextromethorphan
RONDASE: hyaluronidase
Rosacea, 427
Roundworm, 84
Routes of administration, 434–435
ROVAMYCIN: spiramycin
Russell's viper venom, 339

Saccharated iron oxide, 388
Sal volatile, 224
SALAZOPYRIN: sulphasalazine
Salicylamide, 173
Salicylates, 168–173. *See also* Analgesics
  actions, 168–169
  peptic ulcer and, 317
  preparations, 170–171
  toxicity, 171–172
  uses, gout, 180
Salicylazosulphapyridine, 35
Salicylic acid, 418
  mercuric chloride and, 427
  ointment, 418
  sulphur ointment and, 427
Salt restriction, 305
Salt substitutes, 305
SALURIC: chlorothiazide
Salvarsan. *See* Arsphenamine
SALYRGAN: mersalyl
SANDRIL: reserpine
Sarin, 236
  poisoning, 234–235
Sarcoidosis, 99
  vitamin D and, 407
SAVORQUIN: di-iodohydroxyquin
Scabies, 426
Scarlet fever, 56
Schistosomiasis, 83, 86
Schizophrenia, 210, 441
  insulin in, 376
Scleroderma, 99, 427
Scoline: suxamethonium
Scopolamine, 242
Scurvy, 403–404
Seasickness. *See* Motion sickness
SEA-LEGS: meclozine
Seborrheic dermatitis, 427
SECONAL: quinalbarbitone
Secondary effects, 444
SECROSTERON: dimethisterone
Sedative, 101–110
  definition, 101
  poisoning, 109
SEDORMID: apronal
SEDULON, 215
Seidlitz powder, 320
Selenium sulphide, 427
SELSUN: selenium sulphide
Senile vaginitis, 357
Senility, drugs in, 210
Senna, 319, 323, 324, 325
SENOKOT: senna
Sensitivity dermatitis, 426
SEREEN: hyoscine
SERPASIL: reserpine
SERPILOID: reserpine
Serum sickness, 445
Sex and drugs, 440
Sex hormones, 353–360
Shock, 258
Side-effects, 442–448
SIGMAMYCIN: oleandomycin
Silicone creams, 419
Silver nitrate, 418
Simple ointment, 417
Sinusitis, 56, 256
Skin diseases, 416–428
Smallpox, 72

Smoking, 187–188
Sodium, depletion, 305–306
  restriction, 305
Sodium aminosalicylate, 64–68
SODIUM AMYTAL: amylobarbitone sodium
Sodium antimonylgluconate, 82
Sodium aurothiomalate, 177
Sodium bicarbonate, 315
Sodium bromide, 105–107
Sodium calciumedetate, 432
Sodium chloride, uses, cough, 216
    expectorant, 215
Sodium citrate, 62, 315, 337
Sodium hexametaphosphate, 428
Sodium lactate, 302
Sodium nitrite, 264. *See also* Nitrites
  in cyanide poisoning, 432
Sodium potassium tartrate, 319, 320
Sodium radiophosphate, 413, 414
Sodium salicyclate. *See* Salicylates
Sodium sulphate, 319, 320
Sodium tauroglycocholate, 319
Sodium thiosulphate, in cyanide poisoning, 432
SOLPRIN: aspirin, soluble
SOLUPEN: benzylpenicillin
SOLUTHRICIN: tyrothricin
SOMNESIN: methylpentynol
SONERYL: butobarbitone
Sore throats, 55–57
Southey's tubes, 314
SPARINE: promazine
Spasticity. *See* Muscle spasm
Specificity of drug action, 439
Spinal block, 142
Spinal cord depressants, 207
Spiramycin, 51, 54
Spironolactone, 313
Spondylitis, 178
Squill, 162
Squill opiate linctus, 162
Staphylococcal infections, 54–55
Starch, 318
Status asthmaticus. *See* Asthma
Status epilepticus, 115
Steatorrhœa, 407
  adrenocortical steroids in, 99
STELAZINE: trifluoperazine
STEMETIL: prochlorperazine
STENEDIOL: methandriol
STERANDRYL: testosterone propionate
Steroid spirolactones, 313
STIGMONENE: benzpyrinium
Stilbœstrol, 355. *See also* Œstrogens
Stimulants. *See* Antidepressants and Analeptics
Stings, 418–419
Stokes-Adams attacks, 302
STOVAINE: amylocaine
STOVARSOL: acetarsol
Stramonium, 242–243
Streptococcal infections, 55–50
Streptoduocin, 43
Streptokinase-streptodornase, 58
  uses, expectorant, 216
Streptomycin, 41–43
  Gram-staining and, 23
  hypersensitivity to, 67–68
  uses, bronchitis, 57
    brucellosis, 72
    colonic surgery, 61
    dysentery, 61
    endocarditis, 59
    gonorrhœa, 69
    pneumonia, 58
    tuberculosis, 65–68
    typhoid carriers, 45
    urinary infections, 62
Strophanthin K, 289
Strophanthin-G, 289, 290. *See also* Digitalis
Strychnine, 222
  tonics, 7
STYPVEN: Russell's viper venom
SUAVITIL: benactyzine
Substrate competition, 438
Succinylcholine. *See* Suxamethonium
Succinylsulphathiazole, 35. *See also* Sulphonamides
SUCRETS: hexylresorcinol
Sucrose, 313
Suicide, and drugs, 211, 224
Sulphacetamide, 35. *See also* Sulphonamides
  in eye infections, 68
Sulphadiazine, 34. *See also* Sulphonamides
Sulphadimidine, 34. *See also* Sulphonamides
Sulphæmoglobinæmia, 405
Sulphafurazole, 34. *See also* Sulphonamides
Sulphaguanidine, 35

Sulphamerazine, 34. *See also* Sulphonamides
Sulphamethoxypyridazine, 35. *See also* Sulphonamides
SULPHAMEZATHINE: sulphadimidine
Sulphanilamide, 35. *See also* Sulphonamides
Sulphaphenazole, 35. *See also* Sulphonamides
Sulphapyridine, 31
  in dermatitis herpetiformis, 428
Sulpharsphenamine, 80
SULFARSENOL: sulpharsphenamine
Sulphasalazine, 35, 328
Sulphasomidine, 34. *See also* Sulphonamides
SULFASUXIDINE: succinylsulphathiazole
Sulphathiazole, 35. *See also* Sulphonamides
SULFATHALIDINE: phthalylsulphathiazole
SULPHATRIAD: trisulphonamide
SULPHETRONE: solapsone. *See* sulphones
Sulfinpyrazone, 180
Sulfisoxazole. *See* Sulphafurazole
Sulphonal, 108
Sulphonamides, 30–36
  classification, 31–32
  dosage, 34–36
  Gram-staining and, 23
  history, 19
  local analgesics and, 141
  metabolism, 32
  mode of action, 31
  parenteral, 36
  toxic effects, 33
  uses, 33–34
    chancroid, 71
    cholera, 74
    colonic surgery, 61
    enteritis, 61
    meningitis, 60
    staphylococcal infections, 54
    streptococcal infections, 55–56
    ulcerative colitis, 327–328
    urinary infection, 62, 63
Sulphones, 82–83
Sulphur, 323, 427, 428
Sun-burn, 423
Superinfection, 28, 46
Suppositories, 325–326
Suppression of lactation, 357
Suramin, 80–82
SUSTAC, 263
Suxamethonium, 138–139. *See also* Neuromuscular blocking-agents
S.V.C.: acetarsol
Sweating, 268, 428
Sycosis barbæ, 425
Sympatholytics, 266
Sympathomimetics, 249–260
  digitalis and, 286
  fœtus and, 147
  uses, antidepressants, 207–209
    diabetic ketosis, 383
    heart-block, 302
    hypersensitivity reactions, 445
    local analgesics with, 141
SYNCORTYL: deoxycortone
Synergism, 438
SYNKAVIT: vitamin K analogue
SYNTHOVO: hexœstrol
SYNTOCINON: synthetic oxytocin
Syphilis, 69–70
  iodide in, 368

TACE: chlorotrianisene
Tachycardia, 299–300
Tachyphylaxis, 438
Tænia, 84
TAORYL, 215
Tapeworm, 84
Tars, 418
Tea, 225, 227
Teething powders, 324
TEEVEX: crotamiton and halopyramine
TELMID: dithiazanine
TEM, 412
Temporal arteritis, 99
TENORMAL: pempidine
TENSILON: edrophonium
TEPP, 236
  poisoning, 234–235
TERRAMYCIN: oxytetracycline
TESSALON: benzonatate
Test dosing, 447
TESTAFORM: testosterone propionate
Testosterone, 353–354
Testosterone œnanthate, 353–354
Testosterone propionate, 353–354

- *TESTOVIRON:* testosterone propionate
- **Tetanus, 116–119**
  - active immunisation, 116
  - mephenesin in, 206
  - prophylaxis, 116–117
  - treatment, 118–119
- **Tetany,** 408
  - parathyroid in, 406
- **Tetrachloroethylene,** 85
- **Tetracyclines, 46–47**
  - Gram-staining and, 23
  - uses, actinomycosis, 72
    - amœbiasis, 73
    - bronchitis, 57
    - brucellosis, 72
    - chancroid, 71
    - chickenpox, 72
    - cholera, 74
    - dysentery, 61
    - eye infections, 68, 69
    - gonorrhœa, 69
    - granuloma inguinale, 71
    - lymphogranuloma, 71
    - peritonitis, 60
    - pneumonia, 58
    - psittacosis, 58
    - Q fever, 58
    - skin infections, 422
    - streptococcal infections, 54
    - syphilis, 70
    - tetanus, 117, 119
    - typhoid, 45
    - urethritis, 71
    - urinary infections, 62
    - whooping cough, 57
- *TETRACYN:* tetracycline
- **Tetraethylammonium,** 270, 273
- **Tetraethyl pyrophosphate,** 236
  - poisoning, 234–235
- **Tetrahydrozoline,** 256
- **Thalamic pain,** 155
- *THALAZOLE:* phthalylsulphathiazole
- **Thalidomide,** 107
- **Theobromine,** 224–227
- **Theophylline,** 224–227
  - with mersalyl, 307
- *THEPHORIN:* phenindamine
- **Therapeutic trials,** 11–16
- **Thialbarbitone,** 133
- **Thialbarbitone sodium,** 104. *See also* Barbiturates
- **Thiamine.** *See* Aneurine
- **Thiamylal,** 133
- *THIO-BISMOL:* bismuth sodium thioglycollate
- **Thiocyanates,** 369
- *THIOMERIN:* mercaptomerin
- **Thiopentone sodium,** 104, 132–133. *See also* Anæsthetics and Barbiturates in basal narcosis, 131
- **Thiopropazate,** 206
- **Thiotepa,** 412, 414
- **Thiouracil,** 370
- **Thiourea derivatives,** 369–371. *See also* Antithyroids
- *THORAZINE:* chlorpromazine
- **Threadworms,** 84
- **Thrombin,** 337, 338
- **Thrombocytopenia,** 338
  - due to drugs, 446
- **Thromboplastin,** 337
- **Thromboses,** 348
- **Thrush,** 50
- **Thujone,** 224
- **Thyroxine,** 365–367
- **Thyroid,** 365–367
  - crises, 368
  - hormone, versus insulin, 379
- **Thyroid stimulating hormone,** 365
- **Thyrotoxicosis,** 367–374
- **Tics,** amphetamine in, 209
- **Tinea,** 425
- **Tobacco,** 187–188
- *TOCLASE:* carbetapentane
- **Tocopherols,** 408
- *TOFRANIL:* imipramine
- **Tolazoline,** 266–267
- **Tolbutamide,** 383–384
- **Tolerance,** 183, 437–438, 439, 444
- *TOLSERAM:* mephenesin carbamate
- **Tonics,** 7
- **Tonsillitis,** 56
- **Torticollis,** amphetamine in, 209
- **Toxic effects,** 442–448
- **Trachoma,** 69
- **Tragacanth,** 318
- **Tranquillisers, 200–207**
  - definition, 101
  - list of, 203
  - reserpine as, 276, 277
- *TRASENTIN:* adiphenine
- **Travel sickness.** *See* Motion sickness
- **Tretamine,** 412
- **Triac,** 366
- **Trials,** 11–16

Triamcinolone, 92, 93. *See also* Adrenocortical hormones
Tribromoethanol, 131
Trichinella, 85
Trichloroacetic acid, 418
Trichloroethanol, 102
Trichloroethylene, 131. *See also* Anæsthetics
  uses, labour, 147
    pain, 156
Trichomonas, 71
Trichuriasis, 85
Tricyclamol, 244
TRIDIONE: troxidone
Triethanolamine trinitrate, 264. *See also* Nitrates
TRIETHANOMELAMINE: tretamine
Triethylene melamine, 412
Triethylene thiophosphoramide, 412, 414
Trifluoperazine, 206
Trigeminal neuralgia, 154
Tri-iodothyronine, 365–367
TRILAFON: perphenazine
TRILENE: trichloroethylene
TRILLEKAMIN: trimustine
Trimeprazine, 107
Trimetaphan, 273
Trimethidinium, 274
Trimustine, 411, 414
Trinitrin, 263
Trinitroglycerin, 263
TRIOSTAM: sodium antimonylgluconate
Tripelennamine, 335. *See also* Antihistamines
Triple response, 331
Trisulphonamide, 35
TROMEXAN: ethyl biscoumacetate
Tropical diseases, 72–83
Troxidone, 113, 115
Trypanosomiasis, 80–82
Tryparsamide, 80–81
Trypsin, 59
  uses, expectorant, 216
Tryptophan, 402
TSH, 365
TUAMINE: tuaminoheptane
Tuaminoheptane, 256
TUBARINE: tubocurarine
Tuberculosis, 63–68
Tuberculosis—*continued*
  adrenocortical steroids in, 68
  hypersensitivity in, 67–68
  meningeal, 67
  renal, 66–67
  respiratory, 65–66
  skin, 67
Tubocurarine, 136–138. *See also* Neuromuscular blocking-agents
  histamine liberator as, 330
  history, 133
  uses, myasthenic crisis, 238
    tetanus, 119
Tularæmia, 83
Turpentine, 326
Typhoid, 45
Typhus, 83
Tyrocidine, 50
TYRODERM: tyrothricin
Tyrothricin, 50
  in diphtheria, 57
  skin infections, 422
TYZANOL: tetrahydrozoline
TYZINE: tetrahydrozoline

Ulcerative colitis, 327–328
  anticholines in, 244
ULTRACORTEN-H: prednisolone
ULTRACORTENOL: prednisolone trimethylacetate
Undescended testicles, 351
Unna's paste, 418
Unwanted effects, 442–448
Urea, 312
URECHOLINE: bethanechol
Urethane, 412
Urethritis, 71
Urinary infections, 61–63
Urticaria, 333
  due to drugs, 445

Vaginitis, 71
  stilbœstrol in, 357
VAGISEPT: acetarsol
VALLERGAN: trimeprazine
VALLESTRIL: methallenœstril
Vancomycin, 51, 54
VANDID: vanillic acid diethylamide
Vanillic acid diethylamide, 224
Variation, 439
Varicose ulcers, 268

VARIDASE: streptokinase and streptodornase
VASADRINE: isoniazid
Vasodilators, 262–283
Vasopressin, 352–353
Vasopressor drugs. *See* Sympathomimetics
VASOXINE: methoxamine
VASYLOX: methoxamine
VAZADRINE: isoniazid
VEGOLYSEN: hexamethonium
Venereal diseases, 69–71
Venom, cobra, 156
Venous thrombosis, 348
Ventricular fibrillation, 301
Ventricular tachycardia, 300
Veratridine, 278–279
VERATRONE: veratrum
Veratrum, 278–279
VERILOID, 279
Vertigo, 221
VIBAZINE: buclizine
Vincent's angina, 56
VINESTHENE: vinyl ether
VIOCIN: viomycin
VIOFORM: iodochlorhydroxyquinoline, 425
Viomycin, 50, 66
VIRORMONE: testosterone propionate
VIRORMONE-ORAL: methyltestosterone
Vitamin A, 398–399
Vitamin B, 399–403
  deficiency due to tetracyclines, 46
Vitamin B_1. *See* Aneurine
Vitamin B_2. *See* Riboflavine
Vitamin B_6. *See* Pyridoxine
Vitamin B_{12}. *See* Cyanocobalamin
Vitamin C, 403–405
Vitamin D, 405–408
Vitamin E, 408
Vitamin K, 339–340, 345–346
Vitamin K_1, 339–341
Vitamin K analogues, 340
Vitamins, as tonics, 7
Vitiligo, 427
Volatile oils, uses, expectorant, 215
Vomiting, 217–222
VONEDRINE: phenylpropylmethylamine

WARDUZIDE: chlorothiazide
Warfarin, 343, 344. *See also* Anticoagulants
Warts, 418
Wasp stings, 418–419
Water restriction, 306
Waterhouse-Friderichsen syndrome, 95
Weights, 450
Whipworm, 85
White's tar paste, 418, 426
Whooping-cough, 57
Wilson's disease, 432
Worms, 83–86
WYAMINE: mephentermine
WYDASE: hyaluronidase
WYOVIN: dicyclomine

Xanthines, 224–227
  digitalis and, 286
  uses, angina, 265
    diuretic, 311
X-ray dermatitis, 428
XYLOCAINE: lignocaine
XYLOTOX: lignocaine

Yaws, 80, 83
Yohimbine, 268
Young's formula, 434

ZEPH: phenylephrine
Zinc cream, 417
Zinc gelatin, 418
Zinc ointment, 417
Zinc oxide, 417
Zinc oxide and coal tar paste, 418, 426
Zinc oxide and salicylic acid paste, 418, 426
Zinc paste, 418
Zinc stearate powder, 417
Zinc undecenoate, 425
Zoxazolamine, uses, painful muscle spasm, [illegible]
    uricosuric, 180

PRINTED IN GREAT BRITAIN BY THE WHITEFRIARS PRESS LTD
LONDON AND TONBRIDGE

D.S.C.M

17/8/89

25-9-'88

C. F. T. R. I. LIBRARY, MYSORE.

Acc No. 5163

Call No. ~~L:63 K0~~ Lx3 N60

7/5/87

Please return this publication on or before the last DUE DATE stamped below to avoid incurring overdue charges.

VERIFIED 2013

Due Date	Return Date	Due Date	Return Date
28/3/84	28/3/84		
4-5-88	6/5/88		
21.5.88	17.5.88		

Acc. No. 5143
~~2X3 N60~~
63 K0
RENCEAY